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SYNTHETIC STUDIES RELATED TOWARDS THE TOTAL SYNTHESIS OF MEVINOLIN AND COMPACTIN

BY

LOUIS DENNIS HEERZE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled SYNTHETIC STUDIES RELATED TOWARDS THE TOTAL SYNTHESIS OF MEVINOLIN AND COMPACTIN submitted by LOUIS DENNIS HEERZE in partial fulfilment of the requirements for the degree of MASTERS OF SCIENCE.

D. L. J. Clive

(Supervisor)

B. Kratochvil

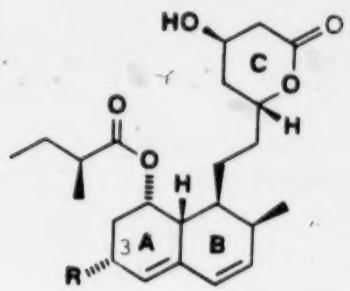
E. E. Kraus

DATE: August 23, 1985

FOR MOM AND DAD

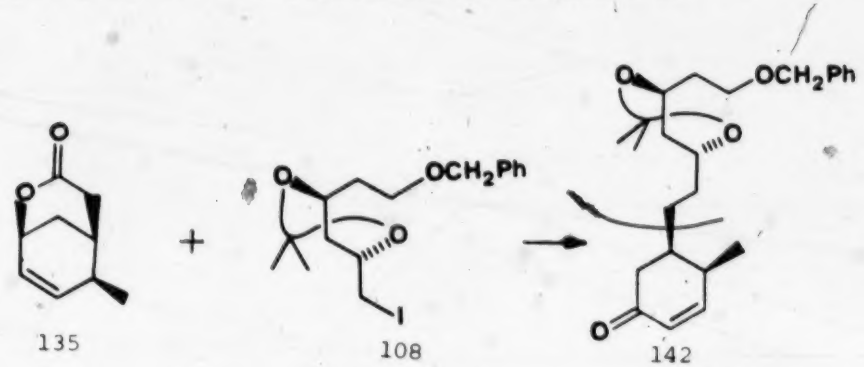
ABSTRACT:

This thesis deals with studies leading towards the total synthesis of the fungal metabolites compactin **1**, and mevinolin **2**, and a synthetic analogue, 3α-ethylcompactin **3**.



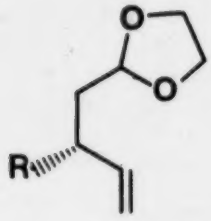
1 R=H
2 R=Me
3 R=Et

An appropriate synthon for ring B, **135**, was prepared, and was coupled by alkylation methodology with optically active iodoketal **108**, which serves as a precursor to ring C. The resulting product, **142**, represents the BC system of the targets **1-3**.



135 108 142

Chiral acetal **150** was prepared by a highly stereoselective alkylation method in which the crucial step (see Scheme 25) depends on the use of an optically active oxazolidone unit as a chiral auxiliary. Acetal **151** was prepared by the same method, but some racemization occurred subsequent to removal of the chiral auxiliary.



150 R=Me
151 R=Et

The thesis also contains a short literature review describing recent synthetic efforts related to the hypocholesterolemic agents **1** and **2**.

ACKNOWLEDGEMENTS

I would like to thank Dr. D.L.J. Clive for his guidance and assistance during the course of my studies, and for his interest and assistance in preparation of this thesis.

My gratitude extends to The University of Alberta for financial assistance in the form of a teaching assistantship.

I would also like to thank the technical service staff in the Department of Chemistry for their help as well as members of my research group who kindly recorded spectra for me.

Finally, I would like to thank the members of my group and my friends for making my studies here an enjoyable experience.

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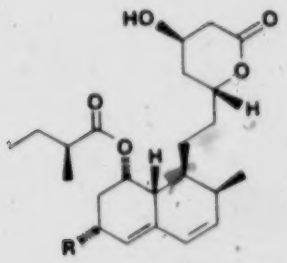
The fungal metabolites mevinolin **2*** and compactin **1**** have very important biological activities and are the subject of considerable journal literature. Both substances have been shown to reduce blood cholesterol levels in mammals,[1] most importantly in man.[5,6]



1 R=H
2 R=Me

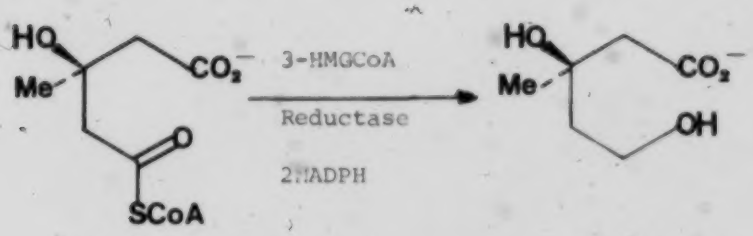
Atherosclerosis, a disease in which fatty deposits build up on the inner walls of arteries, is one of the major factors implicated in the occurrance of heart disease in Western societies.[7] Individuals who have elevated blood cholesterol levels are high-risk candidates for atherosclerosis, and thus, compounds which lower blood cholesterol levels are important in the study of heart disease.

In humans more than 50% of the total body cholesterol is produced via a biosynthetic pathway.[8] If this pathway can be interrupted at some point, then one would have a viable control of blood cholesterol levels.

---

*Mevinolin, isolated from Aspergillustereus,[1] identical to Monakolin K, isolated from Manascusruber.[2] **Compactin and ML-236B, isolated from Penicillium brevicompactin[3] and Penicillium citrinum,[4] respectively.

The major rate-limiting step in the biosynthesis of cholesterol is the two-stage reduction of 3-hydroxy-3-methylglutaryl coenzyme A **4** to mevinolate **5** (Equation 1). Compactin and mevinolin have, in fact, been shown to act as reversible competitive inhibitors of the enzyme, 3-hydroxy-3-methylglutaryl Coenzyme A reductase which is responsible for this reduction.[9]



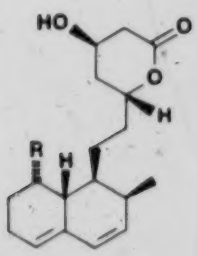
4 5 (1)

It should be noted that the dihydroxy-acid forms of mevinolin and compactin (lactone ring opened) clearly resemble the 3-hydroxy-3-methylglutaryl portion of the enzyme substrate and so the lactone ring is thought to be a biologically important part of the molecule.[11]

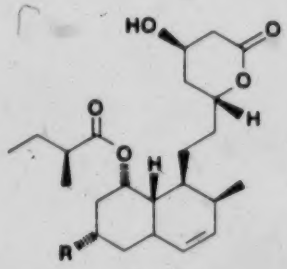
Mevinolin has 3 to 5 times the biological activity of compactin.[1,12] The compounds differ only in that mevinolin has a methyl group at C-3 and so the lactone portions of the compounds are not the only features responsible for biological activity.

Many analogues of mevinolin and compactin have been made both by biological and chemical means. These analogues are important for determining the effects of structure on biological activity in the hope of developing a drug that could be used to treat high blood cholesterol levels.

Some of the analogues obtained from fermentation include metabolites with the ester side chain removed[12] (**6** and **7**), and some dihydroderivatives (**8** and **9**).[13,14]



6 R=H
7 R=OH



8 R=H
9 R=Me

These analogues exhibit lower biological activity than mevinolin or compactin; therefore, the 2-methylbutyrate ester side chain is an important feature in determining biological activity. Microbial oxidation at the 3 or 6 position of mevinolin or compactin produces analogues with 2 to 3 times greater activity.[15,16,17]

Chemical modifications include replacement of the α -methylbutyrate side chain with various ester or ether units.[18-24] The lactone ring has been modified in several ways, which include enlargement to a seven membered ring, forming various salts[25-30] and esters[24,28,31] of the lactone ring-opened dihydroxy-acid, and conversion of the lactone into a mevalinolactone derivative.[24] A number of chemical modifications of the hexahydronaphthalene portion

of mevinolin and compactin have been carried out. All of these modifications centre around the diene system: partial or total reduction,[14,21,26,27] cyclopropanation of one or both of the double bonds,[32] and allylic oxidation.[33] In addition to modifications of the natural products, mevinolin and compactin continue to be an active area of research aimed at total chemical synthesis. Since 1983,* one total synthesis of (±)-compactin,[34] one of (+)-dihydrocompactin,[35] one of (+)-dihydromevinolin,[36] two synthesis of the hexahydronaphthalene portion of compactin,[37,38] and three preparations of the lactone unit[39,40,41] have been published.

The total synthesis of (±)-compactin[34] is based on cis-octalinone **10** (Scheme 1). The approach involves conjugate addition of divinyl cuprate to the least hindered face of cis-octalinone **10** and quenching of the resulting enolate with methyl iodide to yield (85%) alkylated ketone **11**.

Equilibration of the centre alpha to the carbonyl with sodium methoxide in methanol and separation of the isomers gave cis-ketone **12**, which was converted (66%) into **13** by a Shapiro reaction, desilylation, and esterification with racemic 2-methylbutyric anhydride. After elaboration of **13** into **14**, the desired hexahydronapthalene portion was obtained by deprotection of the C-4 hydroxyl of **14** with boron tribromide and dehydration of the resulting alcohol. This sequence gave the diene **15**.

---

*For review up to 1983 see Anderson, P.C., Ph.D. Thesis, University of Alberta.

Hydrolysis of the acetoxy function, oxidation of the resulting alcohol with chromium trioxide, and Wittig olefination gave the required triene **16**. Triene **16** was converted into aldehyde **17** by hydroboration and Collins oxidation. Introduction of the lactone portion involved treatment of aldehyde **17** with diketene-$TiCl_4$ followed by methanol to give a mixture of diastereomeric alcohols **18**. (±)-Compactin was obtained by reduction of **18** to give diol **19** which was cyclized to generate the lactone portion.

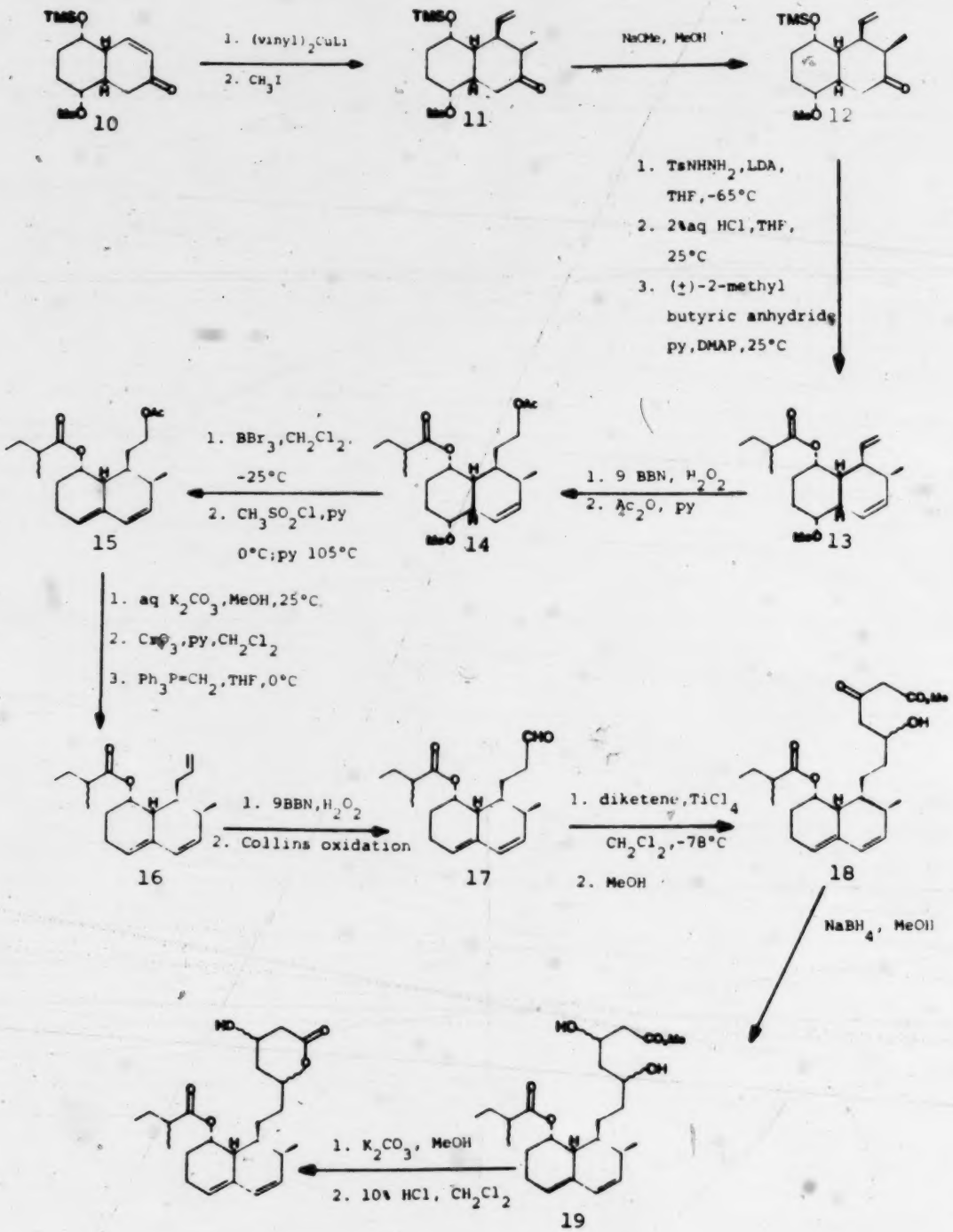
Diels-Alder chemistry has been used a great deal in synthetic work related to compactin and mevinolin. In the total synthesis of (+)-dihydrocompactin,[35] shown in Scheme **2**, the reaction was employed to assemble part of the hexahydronaphthalene portion. The Diels-Alder adduct **22** was elaborated into ketoester **23**, as shown. Protection of the ketone carbonyl and modification of the methoxycarbonyl to a sulfone unit (**23** → **25**) provided the required octahydronaphthalene derivative **25**. This was coupled with sugar-derived iodide **26** using 2 equivalents of base in hexamethylphosphoramide (HMPA). The desired carbon framework had now been formed and it was converted into (+)-dihydrocompactin by the series of straightforward reactions shown in Scheme **2**.

Diels-Alder adduct **29**, made using a sulfoxide, (see Scheme **3**) was used for the synthesis of (+)-dihydromevinolin.[36] Adduct **29**, after acylation, was thermally dehydrosulfenylated with trimethyl phosphite to afford enone **30**. Conjugate addition to the α, ß-unsaturated ketone with dimethyl cuprate provided **31**, which was converted into (+)-dihydromevinolin by the same method used in the synthesis of (+)-dihydrocompactin (see Scheme **2**).

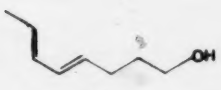
Scheme **4** summarizes an alternative approach[37] to the hexahydronaphthalene portion of compactin. In this case an intramolecular Diels-Alder reaction is employed. Ether **35**, prepared in two steps from **34**, was heated for 2 days at 165°C to give adduct **36** in 69% yield as a mixture of two isomers, which could easily be separated. The resulting tetrahydrofuran moiety was then regiospecifically cleaved with trimethylsilyl iodide to give iodide **37** in 70% yield. This iodide **37** was smoothly converted into sulfone **38.** The hexahydronaphthalene fragment was obtained by low temperature bromination of **38** and dehydrohalogenation with an excess of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU). A mixture of three isomeric dienes was obtained that could be readily separated. The major product proved to be the desired compound **40.**

Another synthesis[38,46] of the hexahydronaphthalene portion of compactin that employs a Diels-Alder reaction is shown in Scheme 5. The reaction of (Z)-ethyl crotonate with Danishefsky's diene gave adduct **41** which, upon reduction, protection, and treatment with base, afforded enone **42** in 72% yield. Conjugate addition of dithiane anion **43** from the less hindered face and subsequent ketal hydrolysis and aldol condensation afforded enone **45** in 74% yield. The required diene functionality could be generated by utilizing a modified Shapiro reaction (**45** → **47**). Deprotection, selective reduction with L-Selectride, and esterification with (S)-2-methylbutyric anhydride gave the hexahydronaphthalene portion of compactin as a mixture of diastereomers that could be separated by HPLC of the chiral (R)-O-methyl mandelyl ester derivatives. An alternative route towards the

Scheme 1

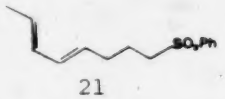

TMSO
MeO
10
1. (vinyl)$_2$CuLi
2. CH$_3$I
11
NaOMe, MeOH
12
1. TsNHNH$_2$, LDA, THF, -65°C
2. 2% aq HCl, THF, 25°C
3. (±)-2-methyl butyric anhydride py, DMAP, 25°C
13
1. 9 BBN, H$_2$O$_2$
2. Ac$_2$O, py
14
1. BBr$_3$, CH$_2$Cl$_2$, -25°C
2. CH$_3$SO$_2$Cl, py 0°C; py 105°C
15
1. aq K$_2$CO$_3$, MeOH, 25°C
2. CrO$_3$, py, CH$_2$Cl$_2$
3. Ph$_3$P=CH$_2$, THF, 0°C
16
1. 9BBN, H$_2$O$_2$
2. Collins oxidation
17
CHO
1. diketene, TiCl$_4$
CH$_2$Cl$_2$, -78°C
2. MeOH
18
CO$_2$Me
OH
NaBH$_4$, MeOH
19
HO
1. K$_2$CO$_3$, MeOH
2. 10% HCl, CH$_2$Cl$_2$

Scheme 2



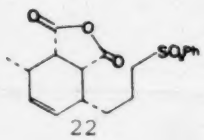
20

1. TsCl, py
2. NaSPh, MeOH, 2h.
3. 2 equiv CH_3CO_3H, EtOAc, -20-0°C, over 2 h.



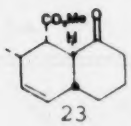
21

maleic anhydride
PhH, 80°C, 24h.



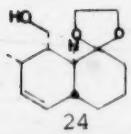
22

1. 2 equiv $LiN(SiMe_3)_2$, THF, -78°C, 5 days, then -40°C, 8h.
2. CH_2N_2
3. Al(Hg), THF/H_2O 10:1, 3h
4. NaOMe, MeOH, 40°C, 24h.



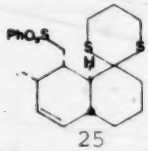
23

1. $(HOCH_2)_2$, p-TsOH PhH, 80°C, 72h.
2. $LiAlH_4$, THF, rt, 72h.



24

1. Me_3SiCl, NaI, CH_3CN
2. $PhSO_2$-Amberlyst A-26 PhH, 80°C, 3h.
3. $HS(CH_2)_3SH$, $BF_3.Et_2O$, CH_2Cl_2, 15h.



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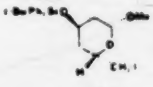
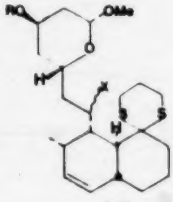


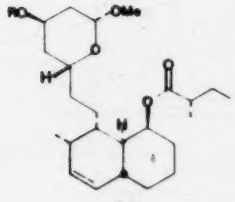
26

1. 2 equiv BuLi, 20% HMPA/THF, 0°C, 30 min.
2. 26, THF, -78°C, warm to room temperature, 4h.



27

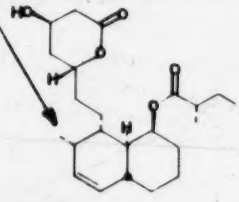
R= t-$BuPh_2Si$
X= SO_2Ph



28

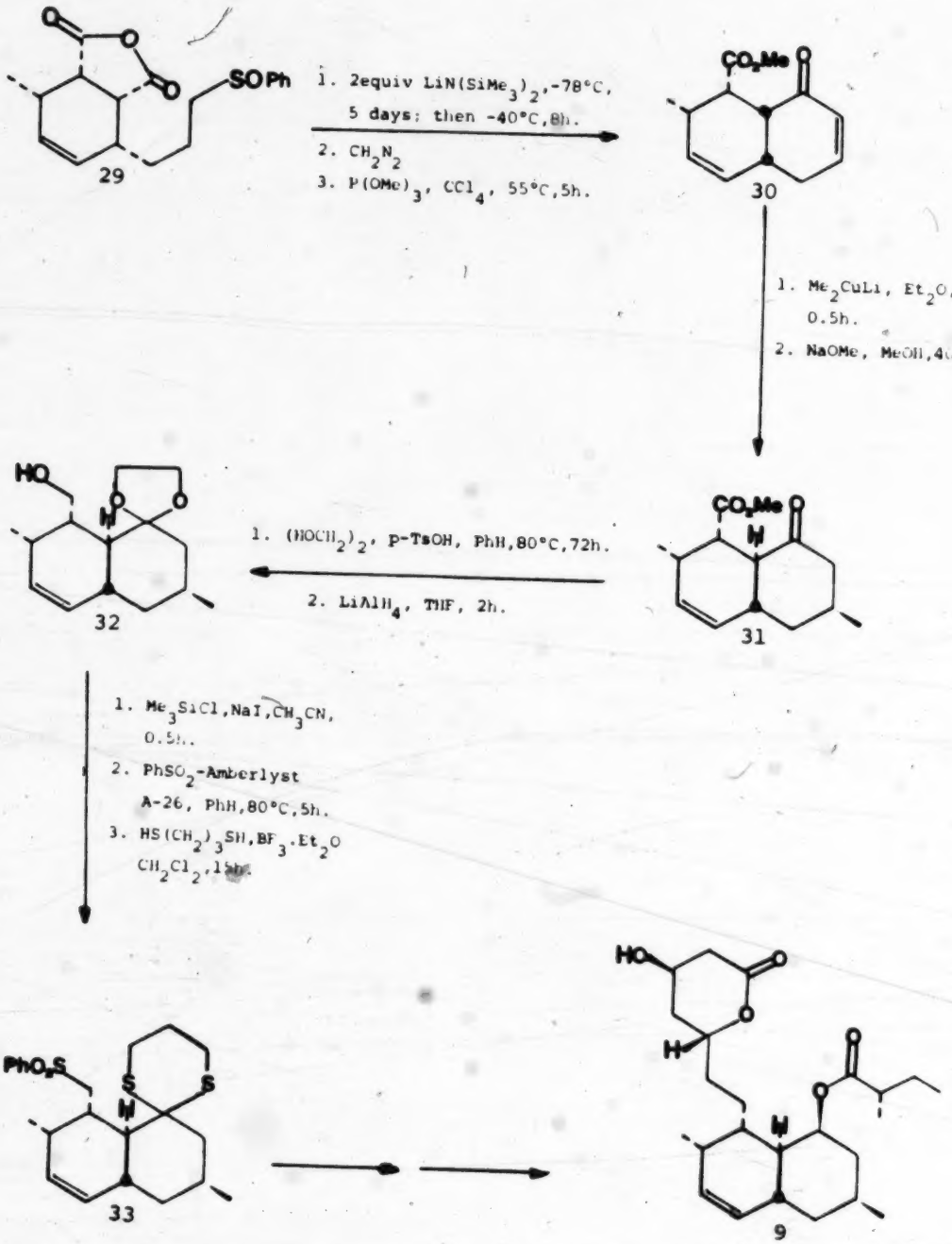
1. $HgCl_2$, $CaCO_3$, CH_3CN/H_2O 4:1 80°C, 7h.
2. 6% Na(Hg), MeOH, 2h.
3. Li(s-Bu)$_3$BH, THF, 0°C, 1h.
4. (S)-(+)-$CH_3CH_2CH(CH_3)CO_2H$, DCC, DMAP, CH_2Cl_2, 24h.

1. 10% HCl/THF 3:5, 45°C, 3.5h.
2. PCC-Al_2O_3, CH_2Cl_2, 8h.
3. 48% HF/CH_3CN 1:10, 45°C, 6h.

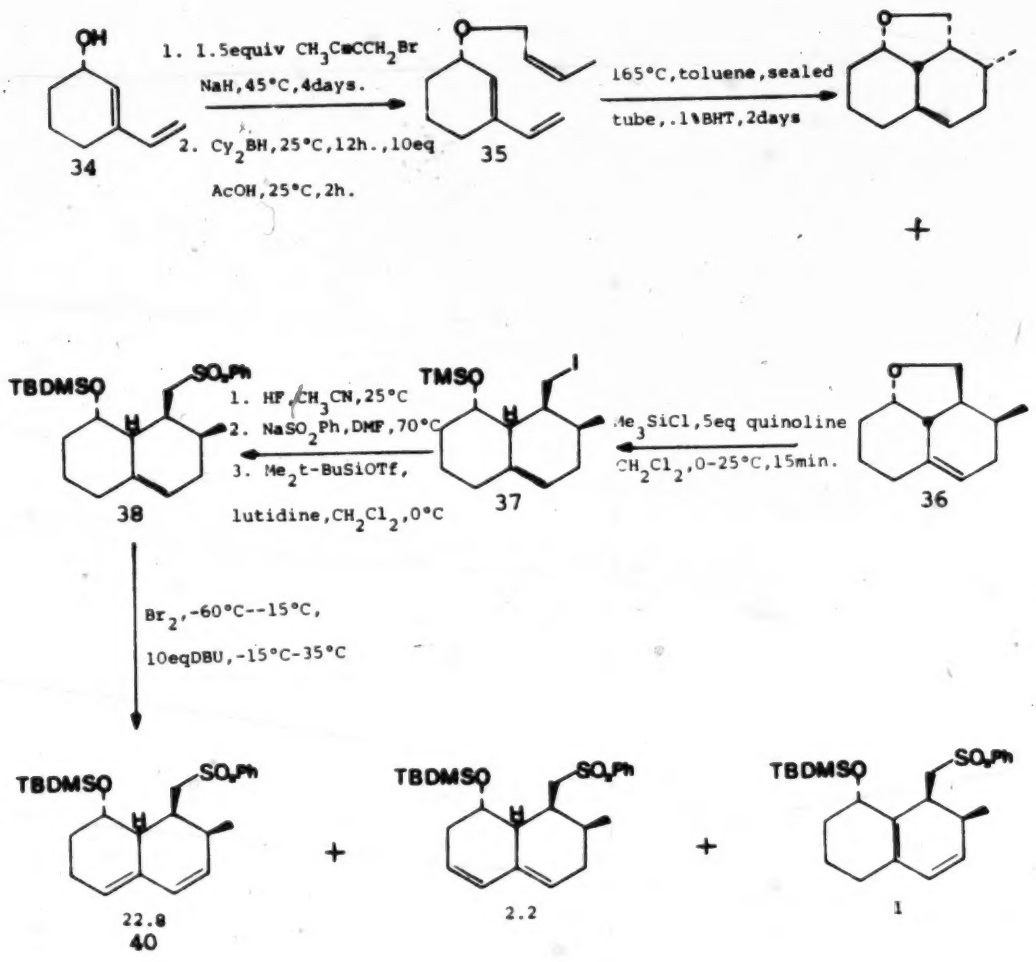


8

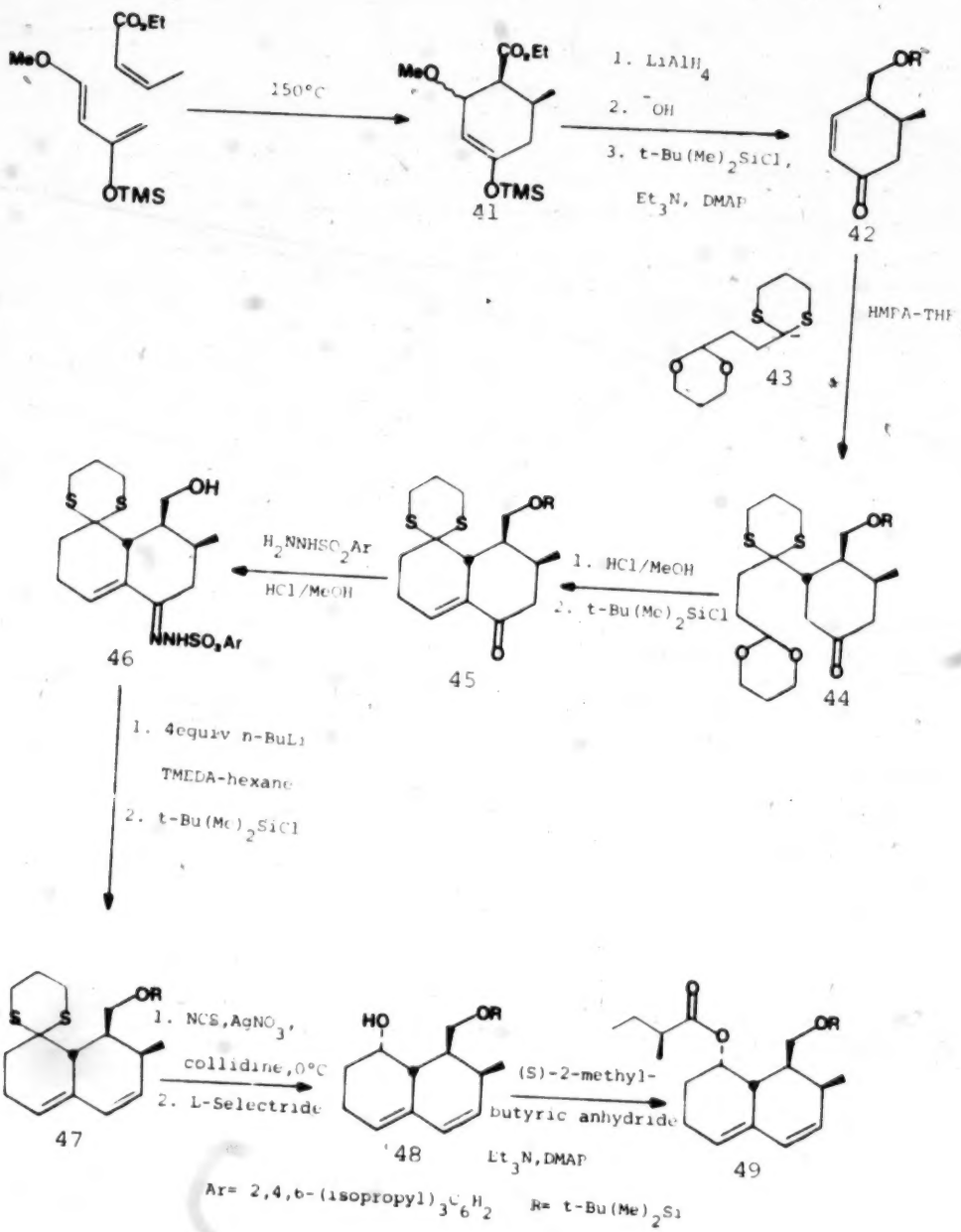
Scheme 3


SOPh
1. 2equiv LiN(SiMe3)2,-78°C, 5 days; then -40°C,8h.
2. CH2N2
3. P(OMe)3, CCl4, 55°C,5h.
CO2Me
1. Me2CuLi, Et2O,0°C, 0.5h.
2. NaOMe, MeOH,40°C,24h.
HO
1. (HOCH2)2, P-TsOH, PhH,80°C,72h.
2. LiAlH4, THF, 2h.
1. Me3SiCl,NaI,CH3CN, 0.5h.
2. PhSO2-Amberlyst A-26, PhH,80°C,5h.
3. HS(CH2)3SH,BF3.Et2O CH2Cl2,15h.
PhO2S
29
30
31
32
33
9

Scheme 4

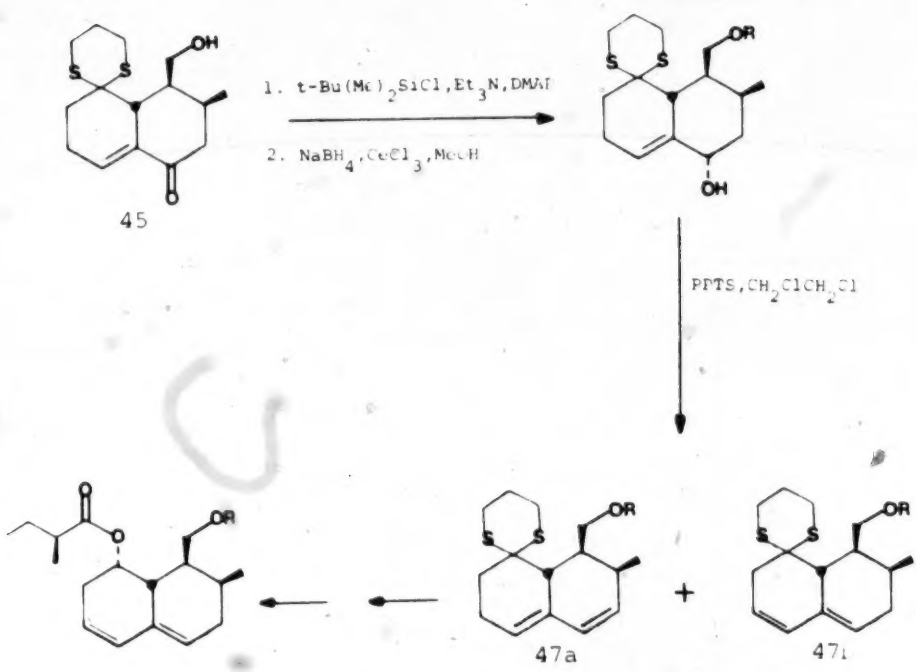

OH
1. 1.5equiv CH_3CCCH_2Br
NaH,45°C,4days.
2. Cy_2BH,25°C,12h.,10eq
AcOH,25°C,2h.
34
35
165°C,toluene,sealed
tube,.1%BHT,2days
+
TBDMSO
SO_2Ph
1. HF,CH_3CN,25°C
2. $NaSO_2Ph$,DMF,70°C
3. Me_2t-BuSiOTf,
lutidine,CH_2Cl_2,0°C
38
TMSO
I
37
Me_3SiCl,5eq quinoline
CH_2Cl_2,0-25°C,15min.
36
Br_2,-60°C--15°C,
10eqDBU,-15°C-35°C
TBDMSO
SO_2Ph
22.8
40
+
TBDMSO
SO_2Ph
2.2
+
TBDMSO
SO_2Ph
1

Scheme 5


MeO
CO2Et
OTMS
150°C
41
1. LiAlH4
2. -OH
3. t-Bu(Me)2SiCl,
Et3N, DMAP
OR
42
43
HMPA-THF
44
1. HCl/MeOH
2. t-Bu(Me)2SiCl
45
H2NNHSO2Ar
HCl/MeOH
OH
NNHSO2Ar
46
1. 4equiv n-BuLi
TMEDA-hexane
2. t-Bu(Me)2SiCl
47
1. NCS,AgNO3,
collidine,0°C
2. L-Selectride
HO
48
(S)-2-methyl-
butyric anhydride
Et3N,DMAP
49
Ar= 2,4,6-(isopropyl)3C6H2
R= t-Bu(Me)2Si

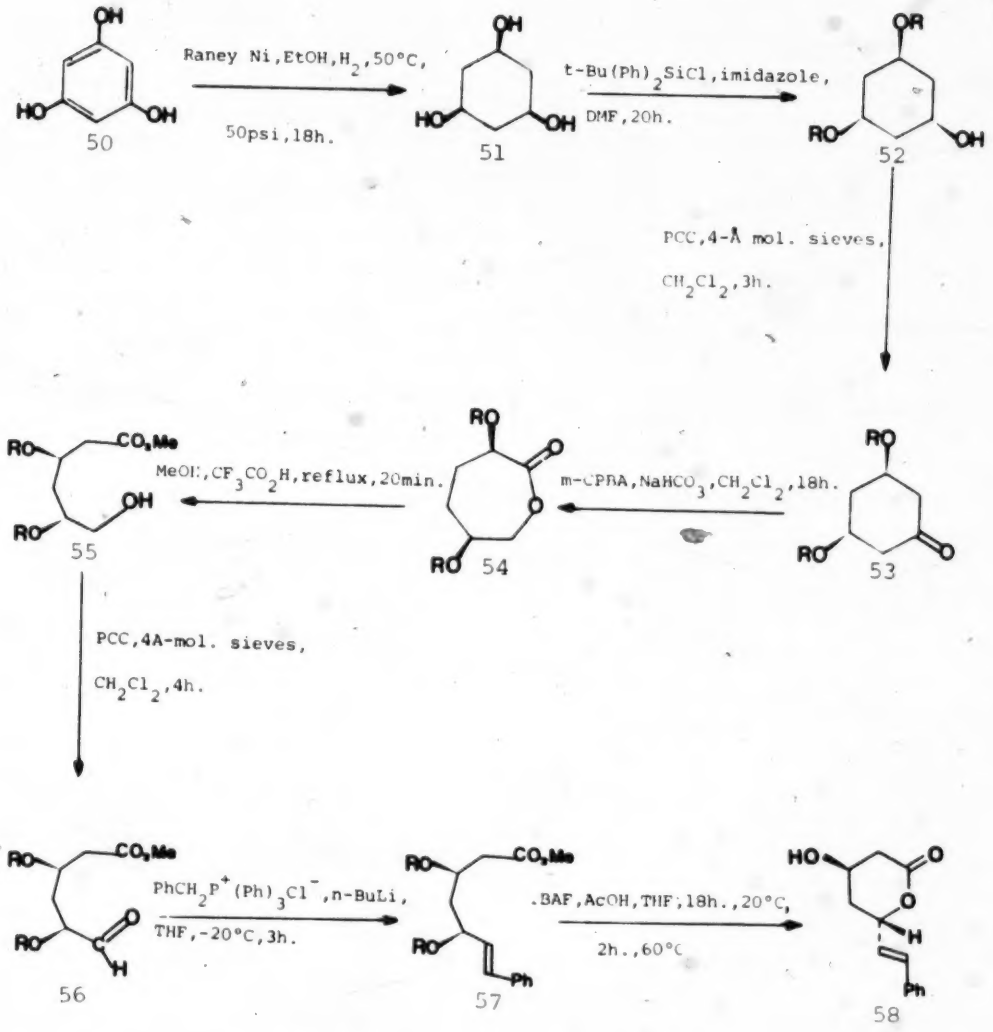
bottom portion of compactin from enone **45** is shown in Scheme 6. The desired **47a** and undesired **47b** isomers were obtained in a ratio of 1:11.[40]

Scheme 6



Three syntheses of the lactone portion have recently been reported. The first one[39] is shown in Scheme **7**, and involves use of 1,3,5-cyclohexenetriol **51.** The triol was readily obtained by hydrogenation of phloroglucinol using Raney Nickel. Protection of two of the hydroxyls and oxidation of the third gave ketone **53** in moderate yield. Baeyer-Villiger oxidation and lactone ring opening under acidic conditions gave hydroxyester **55** in high yield.

Scheme 7

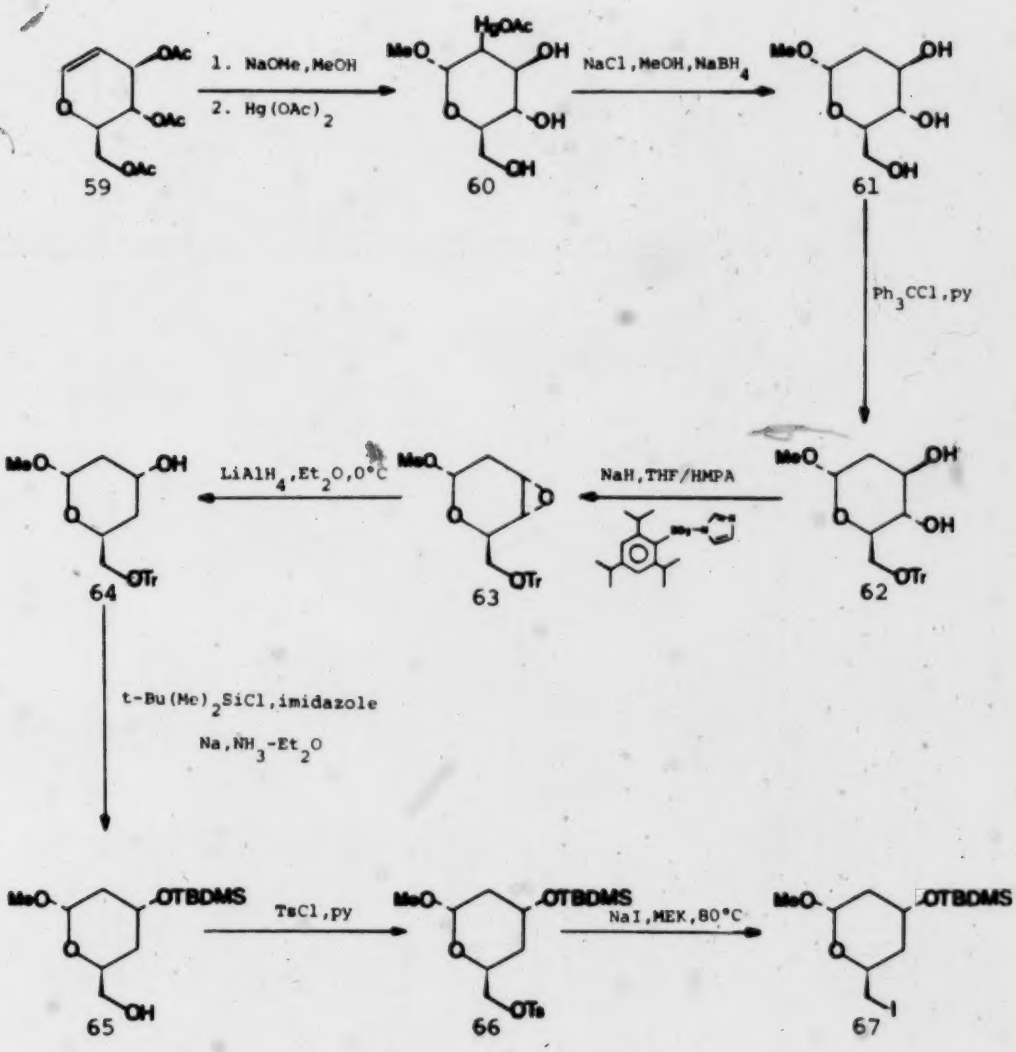

Raney Ni,EtOH,H2,50°C,
50psi,18h.
t-Bu(Ph)2SiCl,imidazole,
DMF,20h.
PCC,4-Å mol. sieves,
CH2Cl2,3h.
m-CPBA,NaHCO3,CH2Cl2,18h.
MeOH,CF3CO2H,reflux,20min.
PCC,4A-mol. sieves,
CH2Cl2,4h.
PhCH2P+(Ph)3Cl-,n-BuLi,
THF,-20°C,3h.
.BAF,AcOH,THF;18h.,20°C,
2h.,60°C
50
51
52
53
54
55
56
57
58

Pyridinium chlorochromate (PCC) oxidation and Wittig olefination then afforded ester **57**. Upon removal of the silyl protecting groups, this compound gave the desired lactone **58**.

A different strategy[40] employed in making the lactone portion, is to use a suitable carbohydrate precursor. In this case, tri-O-acetyl-D-glucal **59** was used (see Scheme **8**) as the starting material. Epoxide **63** was obtained from glucal **59** in 4 steps as shown. The generation of epoxide **63** served three purposes: the unwanted hydroxyl function at C-4 was removed, the stereochemistry at C-3 was inverted to provide the desired 3-β-hydroxy functionality, and finally, an oxygen was introduced, as required, at C-1. Regioselective reduction of epoxide **63** yielded a mixture of alcohols, with the desired axial isomer being the major product. The lactone precursor **67** was obtained by protection of the alcohol, detritylation, tosylation, and displacement by iodide. With the desired iodide and tosylate in hand, various alkylations were attempted with different substrates to explore possible coupling reactions that could be used to link a hexahydronaphthalene portion to the lactone synthons **66** and **67**. However, the results proved to be unpromising.

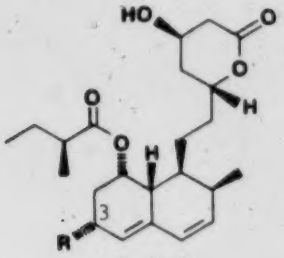
A conceptually different approach to the synthesis of the lactone moeity is by the use of 1,3-dipolar cycloaddition[41] (Scheme **9**). Nitrile oxide **69** and olefin **70** (derived from D-glyceraldehyde) smoothly underwent cycloaddition to form isoxazole **71** as the major product. Upon ketal hydrolysis, cleavage of the diol, protection of the resulting hydroxyl, and hydrogenation of the isoxazole, the masked β-keto-aldehyde **75** was obtained. Treatment of **75**

Scheme 8


1. NaOMe, MeOH
2. Hg(OAc)2
NaCl, MeOH, NaBH4
Ph3CCl, py
NaH, THF/HMPA
LiAlH4, Et2O, 0°C
t-Bu(Me)2SiCl, imidazole
Na, NH3-Et2O
TsCl, py
NaI, MEK, 80°C
59
60
61
62
63
64
65
66
67

with zinc triflate gave the 2,3-dihydropyran-4-one **76** in 85% yield. Reaction of pyran-4-one **76** with methanolic hydrogen chloride gave **77**. Reduction from the least hindered face then afforded <u>erythro</u>-pyranoside **78** in good yield. Isomerization of the methyl pyranoside and removal of the benzyl protecting group furnished pyranoside **80**, which was one of the advanced intermediates in a previous synthesis[40] of the lactone portion (see Scheme 8).

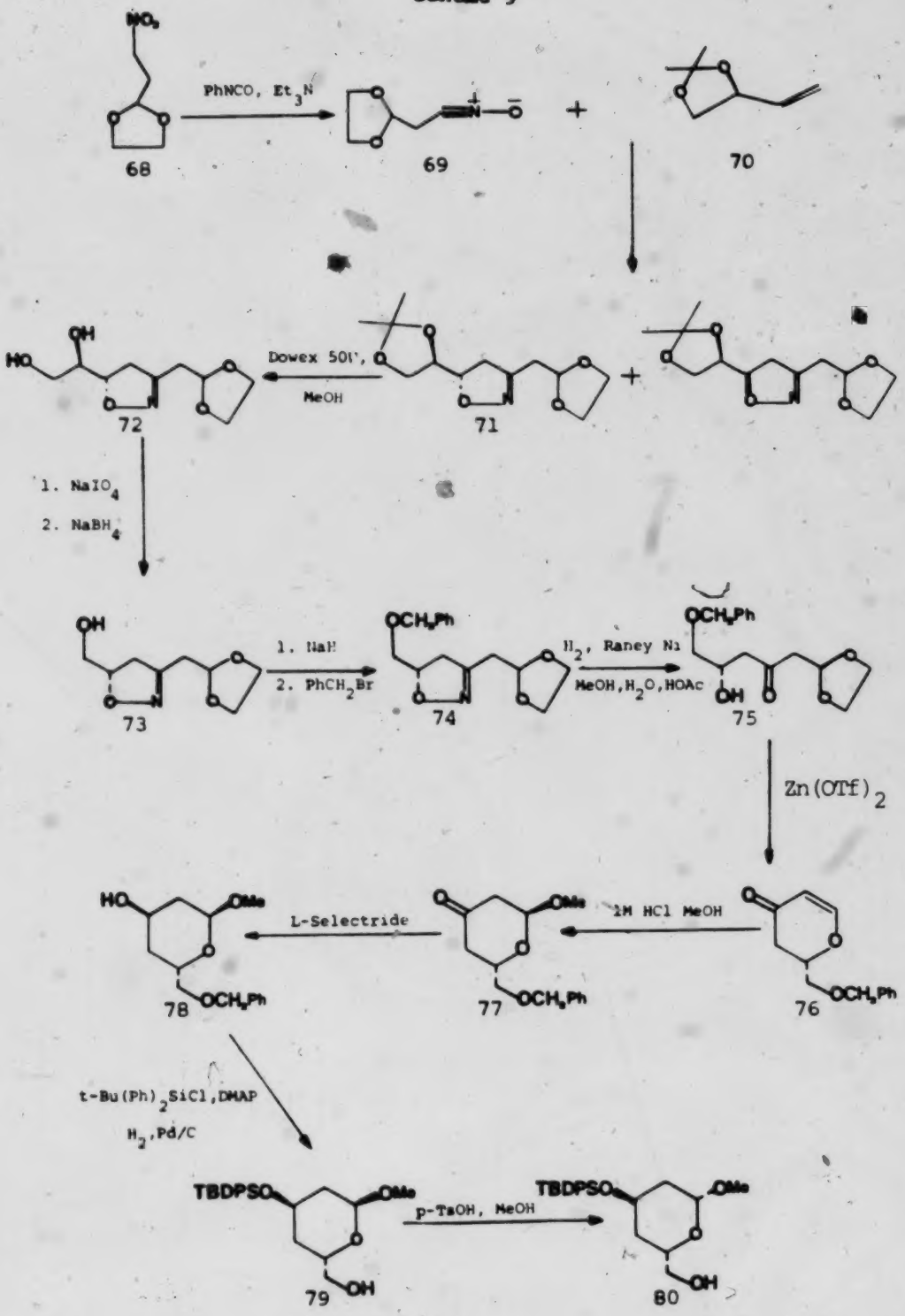
As one can see, the synthesis of mevinolin, compactin, and analogues continues to be of much synthetic interest. When we considered a possible strategy for the synthesis of mevinolin and compactin, we wanted a convergent route, one which would be flexible enough to allow synthesis of analogues, especially those which vary in the substitution pattern of ring A. Mevinolin **2** has been shown to have 3 to 5 times greater activity than compactin **1**.[1,12]



1 R=H
2 R=Me

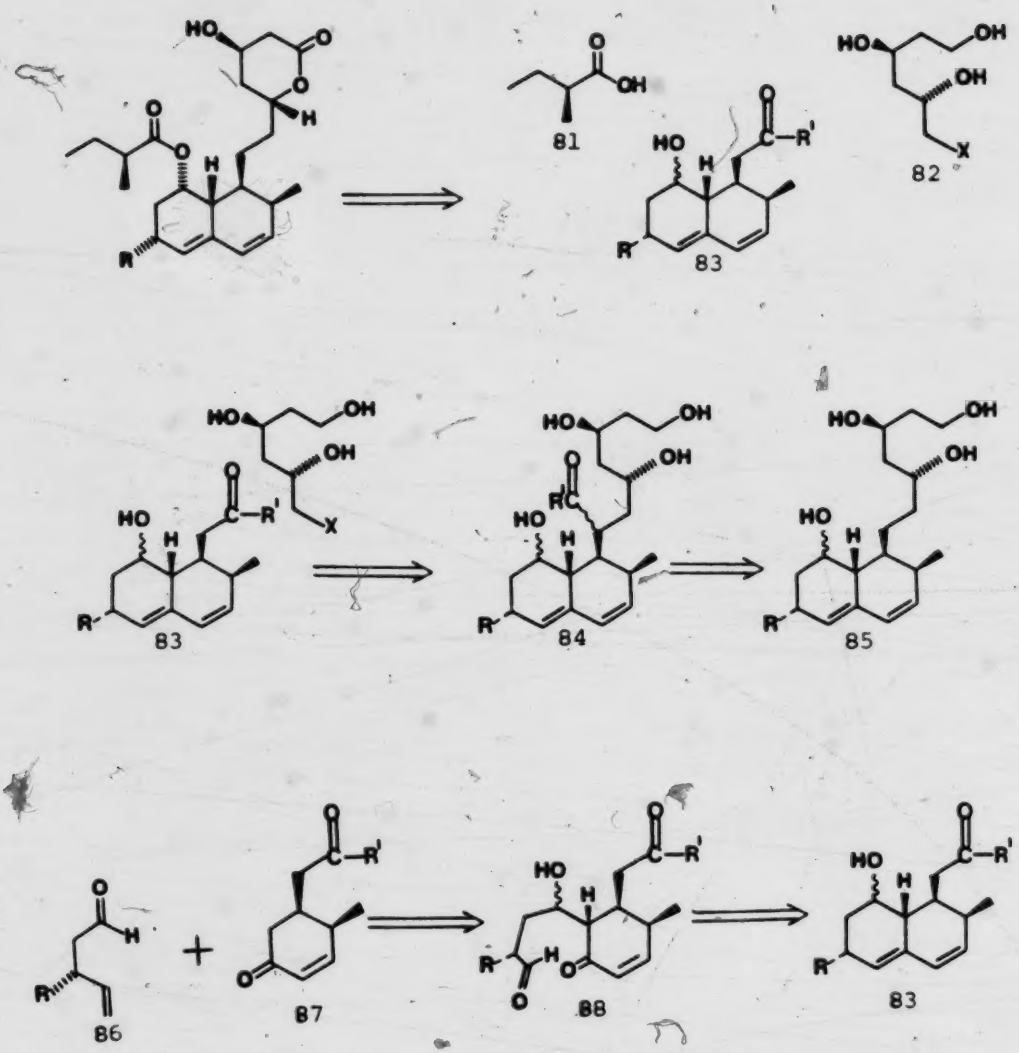
If one were to synthesize analogues in which C-3 was substitued with various other groups (eg. α -ethyl) one could, perhaps, develop analogues with greater biological activity than mevinolin.

Scheme 9

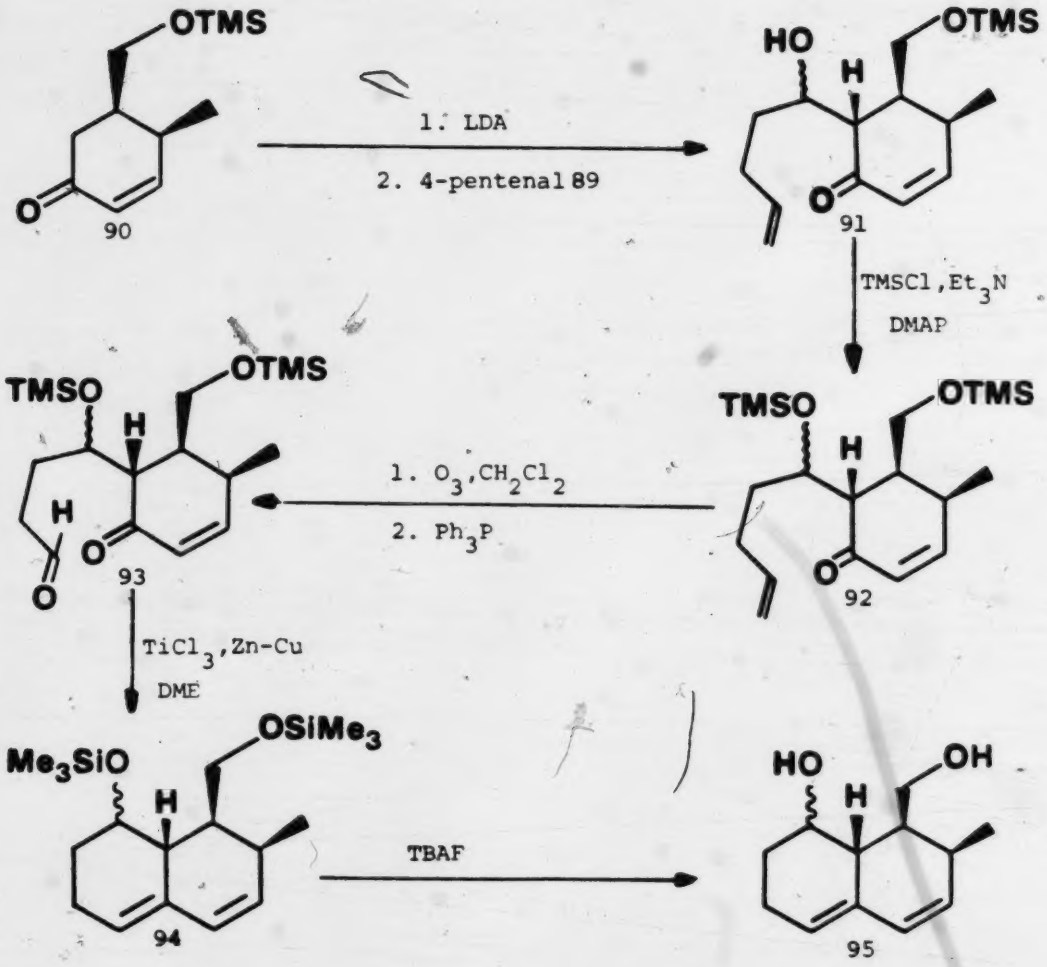

PhNCO, Et3N
68
69
70
Dowex 50W,
MeOH
71
72
1. NaIO4
2. NaBH4
73
1. NaH
2. PhCH2Br
74
H2, Raney Ni
MeOH, H2O, HOAc
75
Zn(OTf)2
76
2M HCl MeOH
77
L-Selectride
78
t-Bu(Ph)2SiCl, DMAP
H2, Pd/C
79
p-TsOH, MeOH
80

Retrosynthetic analysis indicated that these compounds could be constructed from three parts, **81**, **82**, and **83** (see Scheme 10, protecting groups omitted). The α-methylbutyric ester side chain **81** can easily be attached from its commercially available acid chloride. The lactone portion could be synthesized by using the chiral precursor **82**, and an oxidative ring closure would be used to obtain the lactone system. The lactone precursor **82** could be coupled, in principle, to the hexahydronaphthalene unit **83**, by alkylation, and then subsequent removal of the "extra" carbon atom (**84** → **85**). The hexahydronaphthalene portion itself, could be obtained by annulation of a 6-membered ring onto an existing six-membered ring via aldol condensation (**86** + **87**), and carbonyl coupling (**88** → **83**). Part of the plan has been reduced to practice: the hexahydronaphthalene fragment of mevinolin and compactin has been synthesized in our group[47,48] and the route is shown in Scheme 11. Kinetic deprotonation of enone **90** and aldol condensation with aldehyde **89** gave a mixture of diastereomers **91**. The resulting alcohols were protected as trimethylsilyl ethers and the double bond in aldehyde **89** served as a protecting group for the required formyl unit into which it could readily be converted by ozonolysis (**92** → **93**). Low valent titanium coupling[49] provided the desired hexahydronaphthalene product as a mixture of isomers (**93** → **94**).

Scheme 10

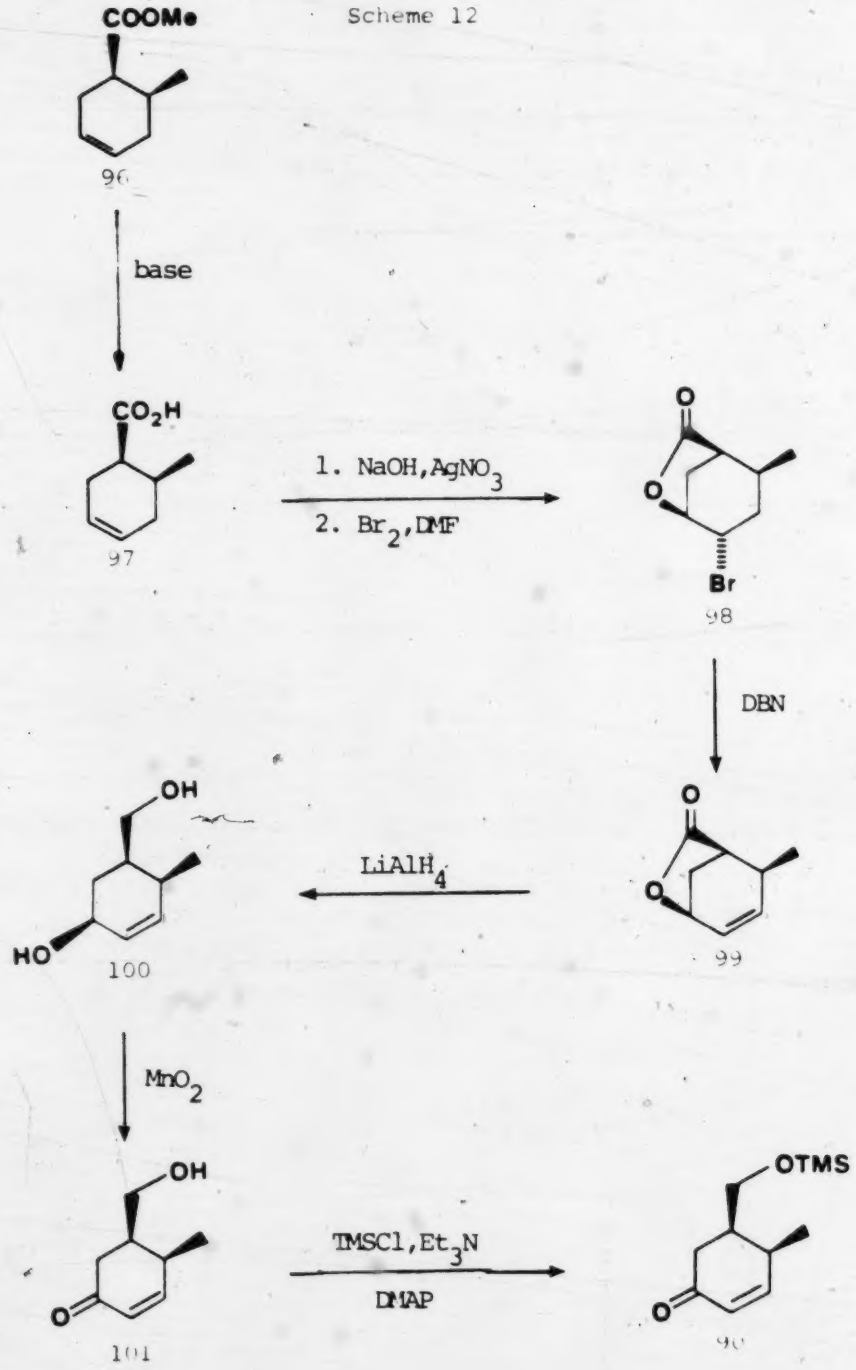

HO
O
O
H
R
81
OH
R'
HO
H
83
HO
OH
OH
X
82
HO
OH
OH
HO
H
R'
X
R
83
HO
OH
OH
HO
H
R'
O
R
84
HO
OH
OH
HO
H
R
85
O
H
R
86
R'
O
87
HO
H
R'
O
R
O
H
O
88
HO
H
R'
R
83

Scheme 11


OTMS
1. LDA
2. 4-pentenal 89
HO
OTMS
H
O
90
91
TMSCl, Et_3N
DMAP
TMSO
OTMS
H
1. O_3, CH_2Cl_2
2. Ph_3P
O
93
92
$TiCl_3$, Zn-Cu
DME
Me_3SiO
$OSiMe_3$
TBAF
HO
OH
94
95

Enone **90**, used in the above sequence, was prepared from cis-ester **96** in 6 steps[47,48] (Scheme 12).

Scheme 12



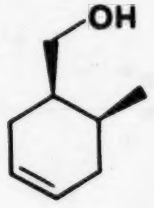
We envisioned that the lactone fragment of mevinolin and compactin could be made from (S)-malic acid (Scheme 13).[50] Generation of the second chiral centre (i.e., at C-5) was achieved by iodocarbonation of homoallylic alcohol **106.** Upon hydrolysis, ketalization, and chromatography, isomerically pure iodoketal **108** was obtained with the two chiral centres required for the final lactone. Iodoketal **108** was coupled with model sulfone **109** and elaborated to the desired lactone **116**[50] (see Scheme 14).

At this point in our synthesis we now had the methodology to assemble the hexahydronaphthalene portion as well as a synthesis of the lactone unit, and so we concentrated on possible modes of coupling the two fragments.

The first idea examined was anionic attack on an epoxide as shown in Scheme 15.

Epoxide **118** can be prepared by treatment of iodoketal **108** with base.

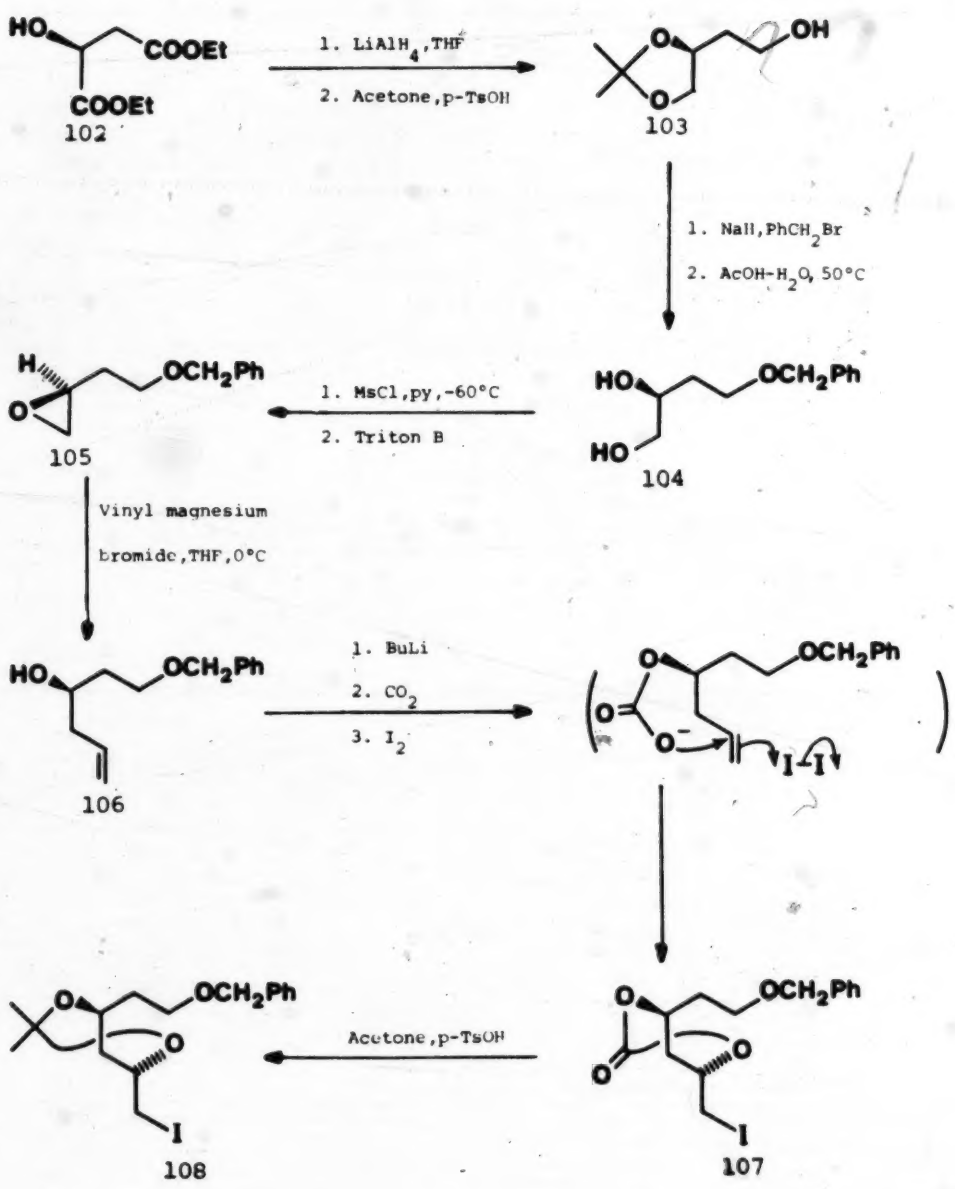
For model studies we used a suitable precursor to ring B, namely alcohol **119** that could be easily converted to a number of



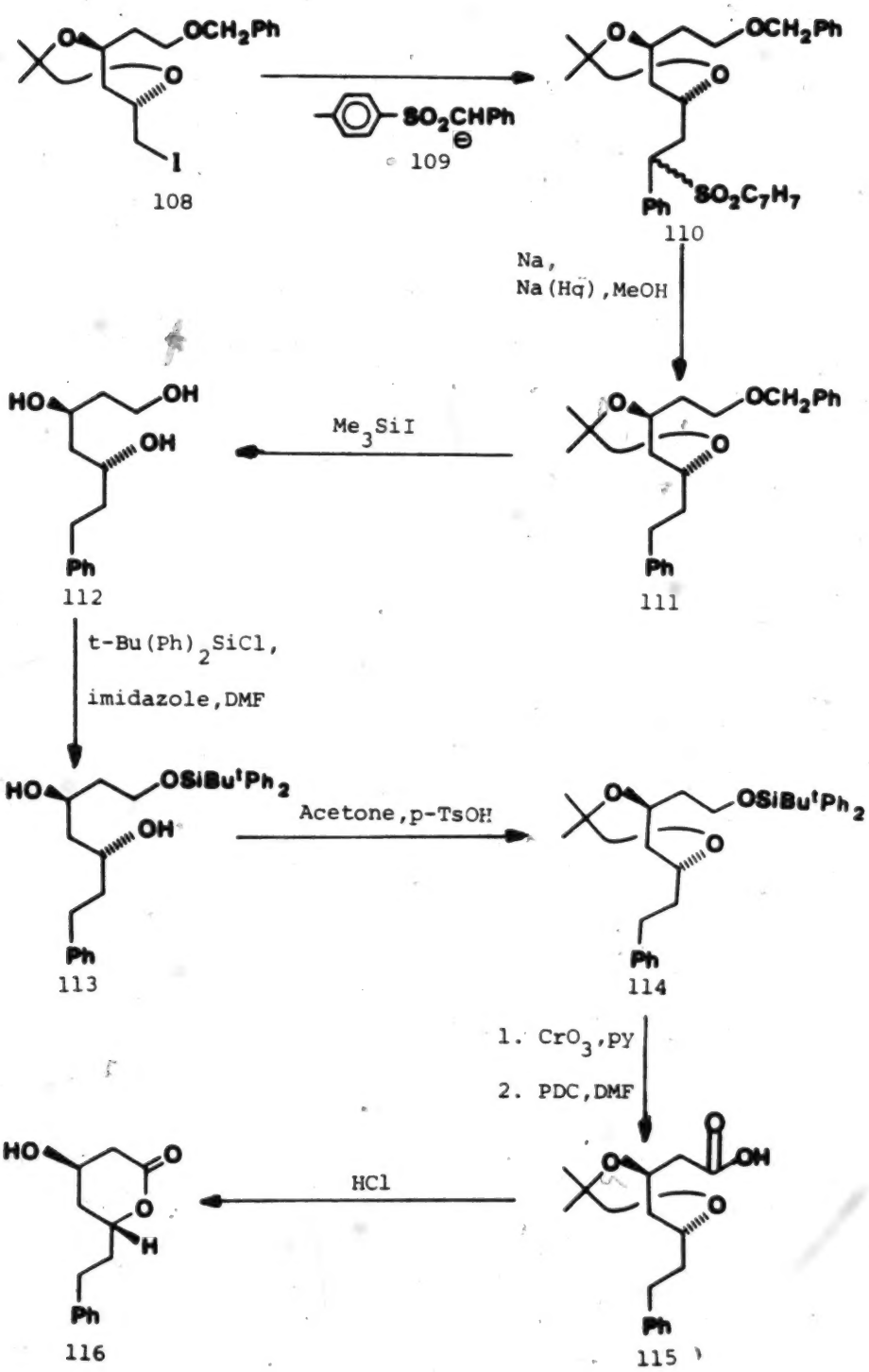
119

different substrates. Bromide **120** was easily made from the alcohol **119**, but no Grignard reagent could be prepared. Attempts

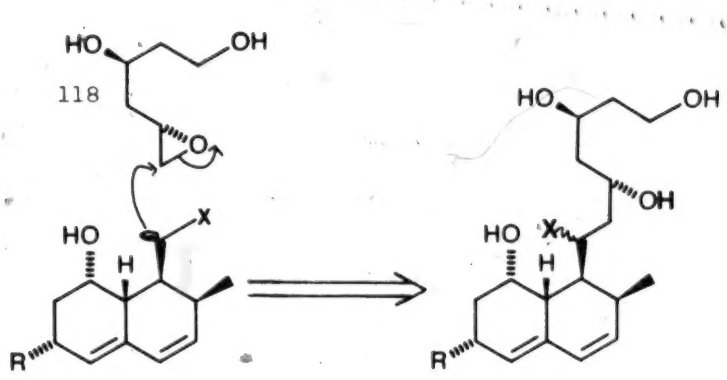
Scheme 13


HO
COOEt
COOEt
102
1. LiAlH4,THF
2. Acetone,p-TsOH
OH
103
1. NaH,PhCH2Br
2. AcOH-H2O, 50°C
HO
OCH2Ph
HO
104
1. MsCl,py,-60°C
2. Triton B
H
OCH2Ph
105
Vinyl magnesium
bromide,THF,0°C
HO
OCH2Ph
106
1. BuLi
2. CO2
3. I2
OCH2Ph
I
I
Acetone,p-TsOH
OCH2Ph
I
108
OCH2Ph
I
107

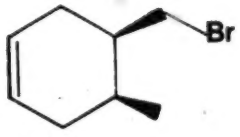
Scheme 14


OCH2Ph
I
108
SO2CHPh
109
OCH2Ph
SO2C7H7
Ph
110
Na,
Na(Hg),MeOH
HO
OH
Ph
112
Me3SiI
OCH2Ph
Ph
111
t-Bu(Ph)2SiCl,
imidazole,DMF
HO
OSiBu'Ph2
OH
Ph
113
Acetone,p-TsOH
OSiBu'Ph2
Ph
114
1. CrO3,py
2. PDC,DMF
HO
O
O
H
Ph
116
HCl
OH
O
Ph
115

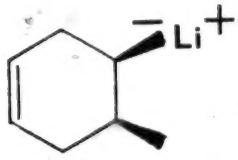
Scheme 15



to prepare the lithium salt **121** from the bromide proved also to be unsuccessful.

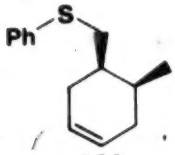


120

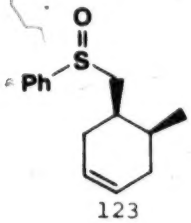


121

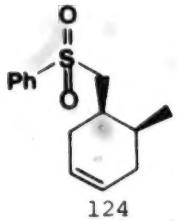
We now turned our attention to the use of stabilized anions for the coupling reaction. Sulfide **122** was oxidized to the sulfoxide **123** and to the sulfone **124** but these compounds, after



122



123

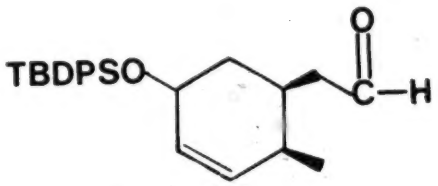


124

deprotonation, also proved to be uncreative towards epoxide **118** and iodoketal **108.** We attributed the unreactivity to the structurally crowded environment of the anion.

At this stage we decided to try Corey's modification of the Wittig reaction.[51] By this reaction we could join a carbonyl carbon of an aldehyde, an electrophilic carbon of an epoxide, and the carbon from an ylide. The resulting homoallylic alcohol with one of the desired chiral centres could then be used to generate the second centre of chirality by iodocarbonation, and then finally elaborated to the lactone (see Scheme 16).

Chiral epoxide **105** was treated with lithiated Wittig reagent to form **126.** Aldehyde **127** was then added to α-Hydroxy Wittig reagent **126** and gave coupled product **128** (26%) of undetermined stereochemistry. This result represented a possible mode of coupling, but when the reaction was examined with a more suitable aldehyde **130**, no coupled products were obtained.* The apparent



130

lack of coupling is not understood.

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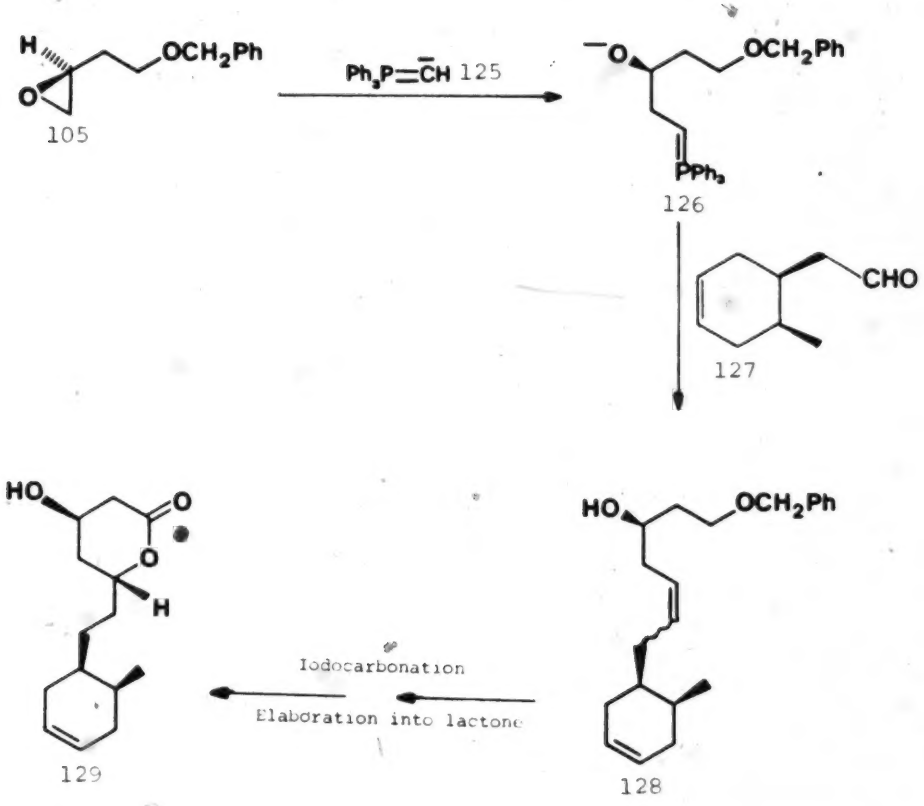
*This work was performed by Dr. M. Majewski.

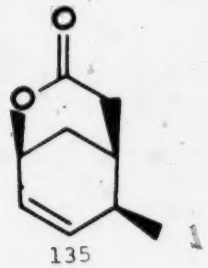
Scheme 16



At this point of the synthesis of mevinolin and compactin we turned our attentions to possible alkylations of iodoketal **108** and a suitable compound that could serve as a synthon for the right hand portion of the hexahydronaphthalene system (Ring B).

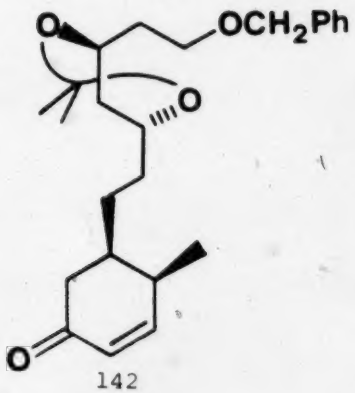
The topics that will be discussed in the Results Section of this thesis are:

1. Preparation of a suitable carbonyl compound that could be used in alkylation of iodoketal **108**. The compound chosen is bicyclic lactone **135**.



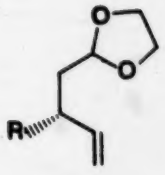
135

2. Coupling reactions of lactone **135** and iodoketal **108** and elaboration into compound **142**.



142

3. Preparation of optically active aldehydes **150** and **151** that will be used as synthons for ring A in making mevinolin and 3α-ethylcompactin.

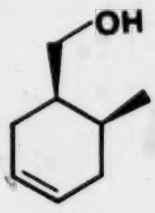


150 R=Me
151 R=Et

RESULTS AND DISCUSSION

The appropriate ring B synthon **135** was prepared from cis-ester **96** as shown in Scheme 17. The racemic cis-ester **96** was made by the method summarized in Scheme 18.[52,53] Trans-acid **136**, which can be easily prepared by a Diels-Alder reaction between butadiene and (E)-crotonic acid,[53] was converted into its sec-butyl ester via the acid chloride. Upon hydrolysis with KOH in boiling ethylene glycol a 50:50 mixture of cis and trans acids **138** was obtained. Esterfication with dimethyl sulfate and potassium carbonate gave the corresponding cis and trans esters which could easily be separated by spinning band distillation. The cis ester **96** has also been made by other methods, but these we deemed impracticable since only by the Diels-Alder route could the cis material be made inexpensively in large batches from readily accessible starting materials.

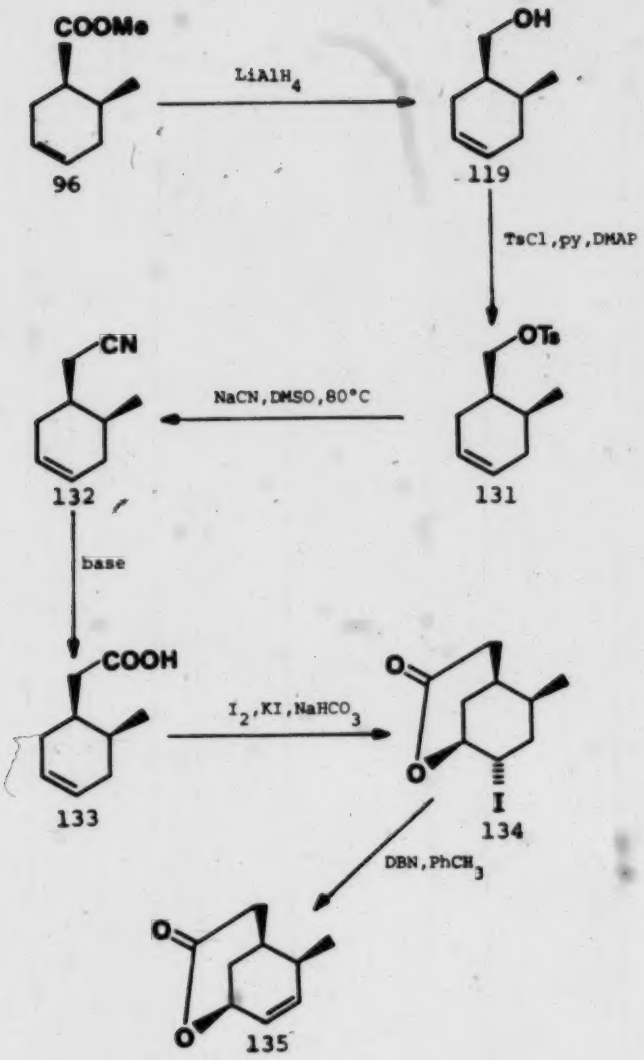
The cis ester **96** was converted (97%) into alcohol **119** by lithium aluminum hydride reduction[54] and the alcohol was



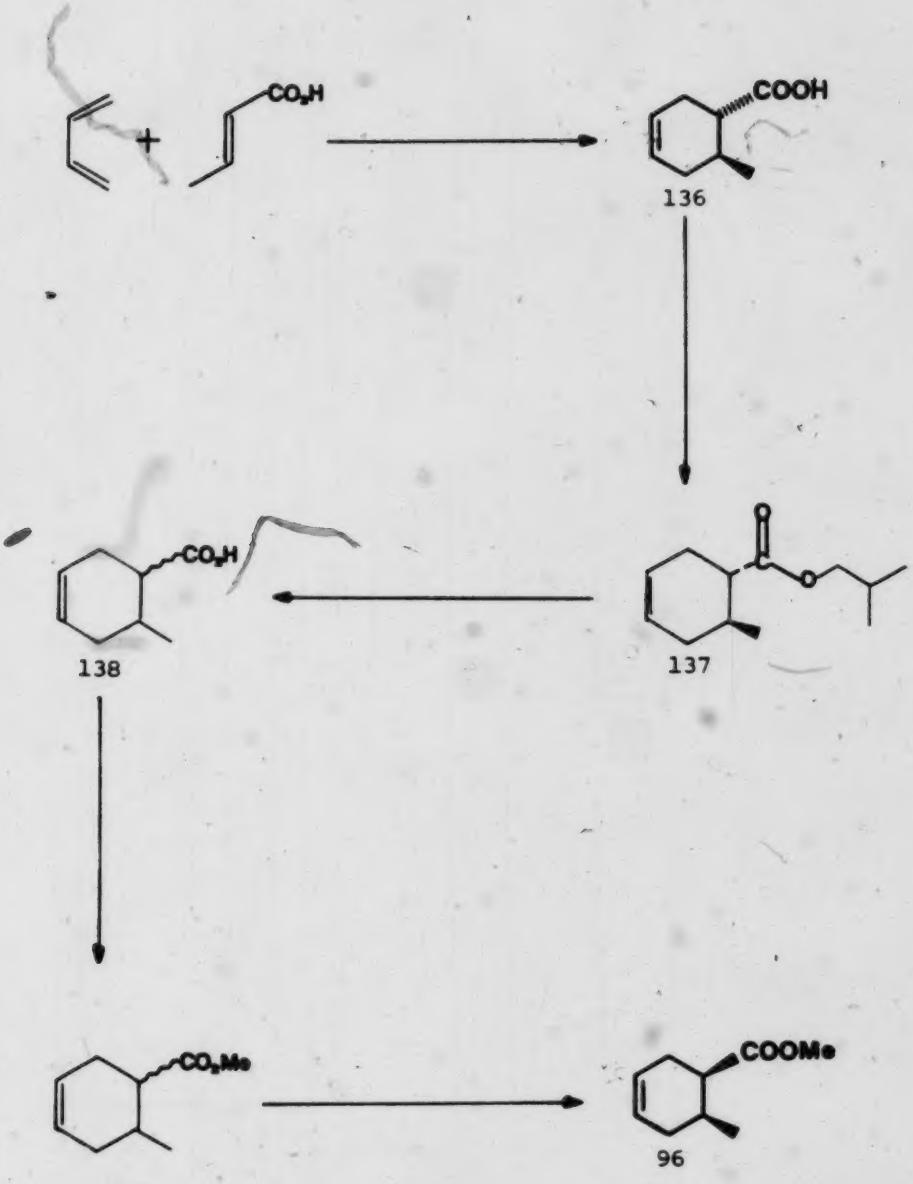
119

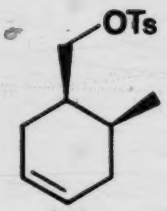
transformed (85%) into tosylate **131** by the action of p-toluenesulfonyl chloride and pyridine, the tosylaton being catalysed by dimethylaminopyridine (DMAP).

Scheme 17


COOMe
LiAlH4
OH
96
119
TsCl,py,DMAP
CN
NaCN,DMSO,80°C
OTs
132
131
base
COOH
I2,KI,NaHCO3
O
O
I
133
134
DBN,PhCH3
O
O
135

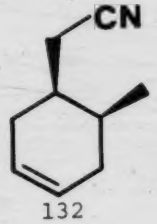
Scheme 18





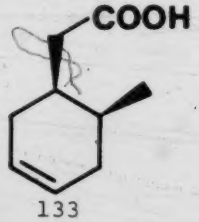
131

Nucleophilic displacement of the tosylate with sodium cyanide in DMSO at 80°C provided the nitrile **132** in 86% yield.



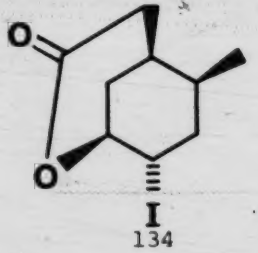
132

This compound was hydrolysed to afford the homologated acid **133** in 93% yield.



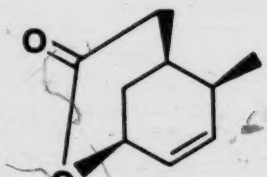
133

Iodolactonization[55] with sodium bicarbonate, potassium iodide, and iodine provided the bicycloiodolactone **134** (80%).



134

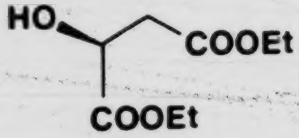
Dehydrohalogenation by treatment with 1,5-diazabicyclo [4.3.0] non-5-ene (DBN) in refluxing toluene then gave the olefinic lactone **135** in 87% yield.



135

No ε lactone products were observed in the final recrystallized material and the substance was homogeneous as judged by thin layer chromatography and ^{1}H and ^{13}C NMR measurements.

With the lactone **135** in hand, iodoketal **108** was prepared as outlined in Scheme 19.[50,56] (S)-Malic acid was converted almost quantitatively into its diethyl ester **136** (98%).

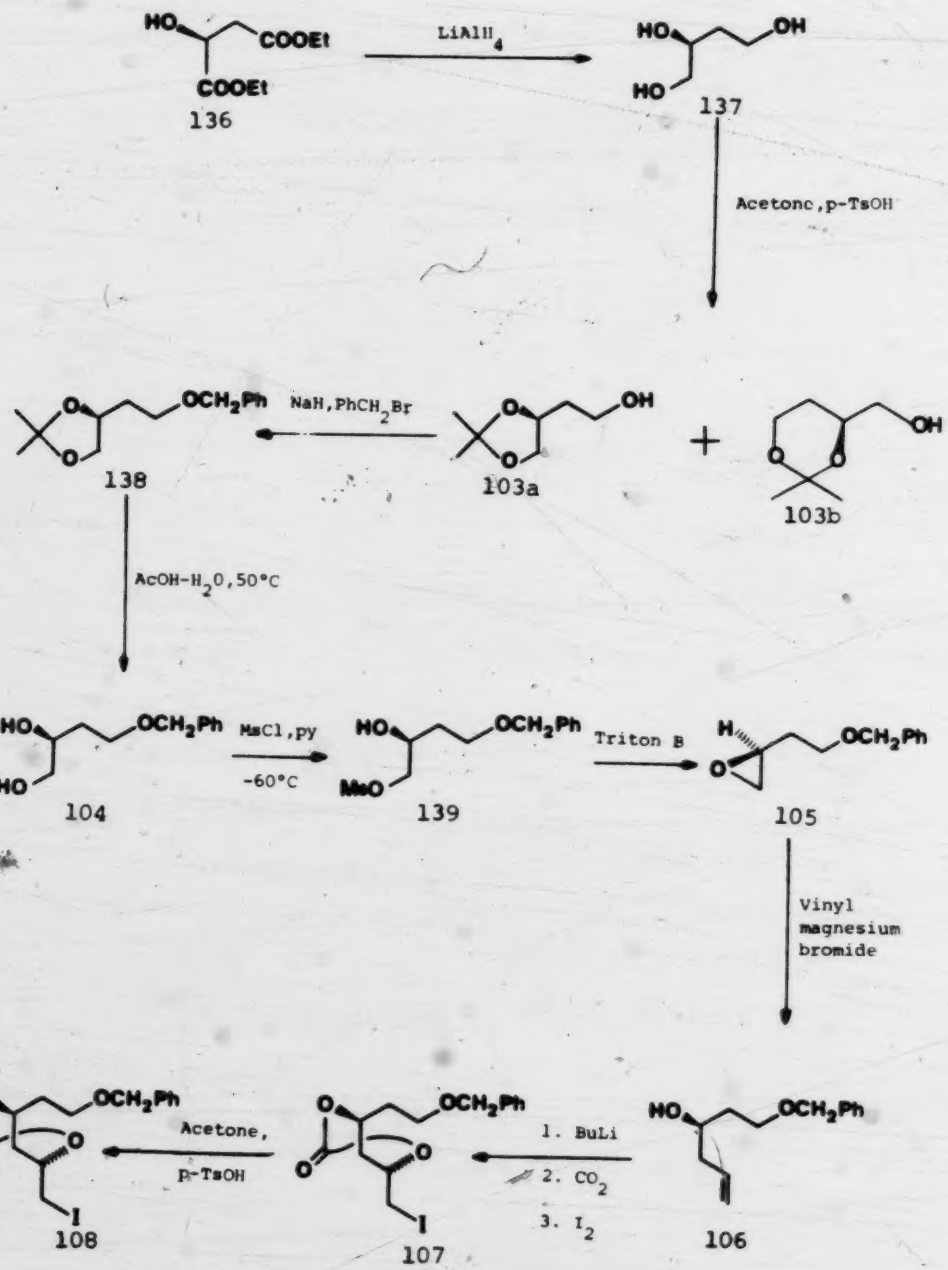


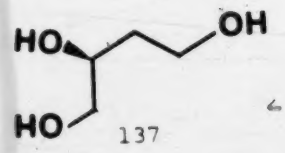
136

Reduction of **136** with lithium aluminium hydride gave the triol **137**[58] in moderate yields (51%). Recently it has been reported that (S)-malic acid can be converted directly into the triol in good yields by borane-methyl sulfide complex.[59]

With the triol **137** in hand, it was an easy matter to protect the 1,2-diol as an acetonide. This was achieved by treating the triol in acetone with a catalytic amount of p-toluenesulfonic acid.

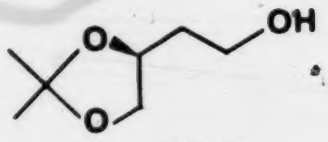
Scheme 19


HO
COOEt
COOEt
136
LiAlH4
HO
OH
HO
137
Acetone, p-TsOH
OCH2Ph
NaH, PhCH2Br
OH
138
103a
103b
AcOH-H2O, 50°C
HO
OCH2Ph
HO
104
MsCl, PY
-60°C
MsO
139
Triton B
H
OCH2Ph
105
Vinyl magnesium bromide
Acetone, p-TsOH
108
1. BuLi
2. CO2
3. I2
107
106

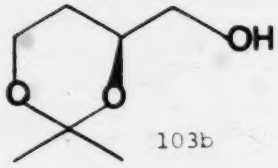


137

The product obtained in 86% yield was a mixture of **103a** and **103b** in the ratio of 9:1.

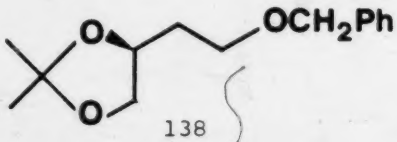


103a



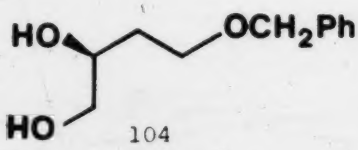
103b

The mixture of acetonides were used as such and the primary hydroxyl was protected by benzylation.[61]



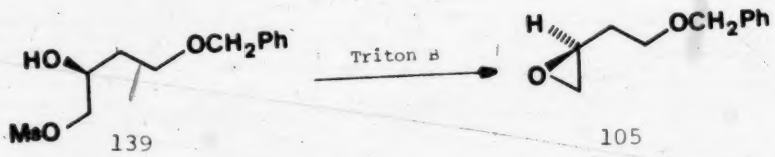
138

Hydrolysis of the acetonide with aqueous acetic acid gave diol **104** in 90% yield.[61]



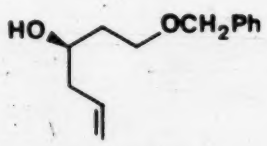
104

Selective mesylation of the primary hydroxyl under carefully controlled conditions gave the monomesylate **139.** The crude material was treated directly with Triton B (N-benzyltrimethylammonium hydroxide) in ether to generate epoxide **105** in 65% from **104.**



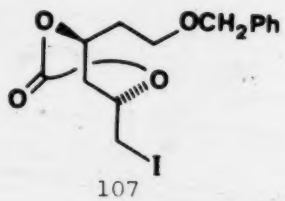
139 105

Treatment of the epoxide with vinyl magnesium bromide in THF proceeded very smoothly and gave the homoallylic alcohol **106** in 99% yield. This alcohol contained only one of the two asymmetric centres



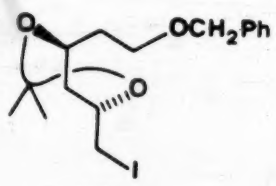
106

present in the lactone portion of compactin and mevinolin and, at this point we had to induce the second centre of chirality. Homoallylic alcohol **106** was treated with n-butyl lithium to form the anion, carbon dioxide was bubbled through the solution, and, finally, a solution of iodine was added.[62,63] The iodocarbonate **107** was obtained as a mixture (erythro:threo 9:1) in 69% yield. The ratio of erythro:threo was easily determined by NMR measurements.



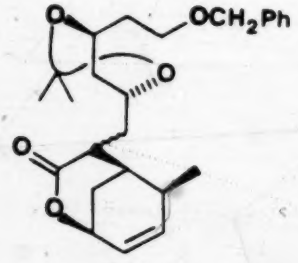
107

Iodocarbonate **107** proved to be very sensitive towards light, and so it was converted directly into iodoketal **108** with dry acetone and one equivalent of p-toluenesulfonic acid monohydrate. Upon purification of the crude reaction product a single isomer was obtained in 63% yield.



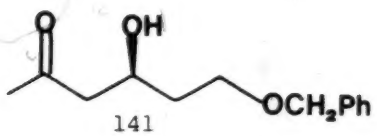
108

At this stage we now had racemic lactone **135** and iodoketal **108** in hand and so we attempted the crucial coupling reaction. Treatment of the racemic lactone **135** with two equivalents of lithium diisopropylamine (LDA) and addition of optically active iodoketal **108** at -78°C in the presence of a 20% v/v solution of HMPA or DMPU[64] in THF gave coupled product **140** in 65% yield (74% based on recovered starting lactone) as a mixture of diastereomers.



140

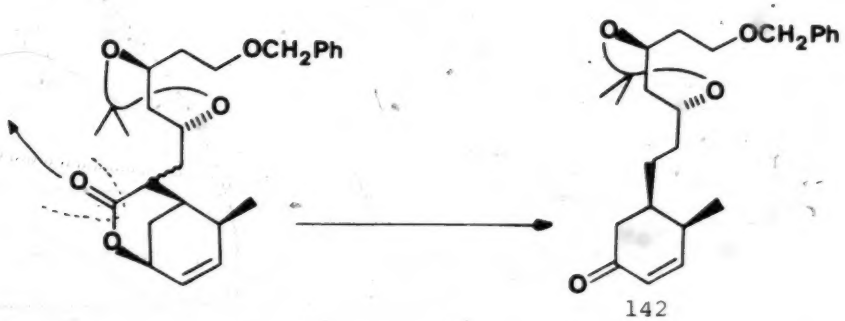
Other than recovered starting material the only side product from the reaction was one in which elimination had taken place from the iodoketal to produce ß-hydroxy-ketone **141**.



141

To obtain the desired enone **142** we needed to remove the "extra" carbonyl carbon (see Scheme 20).

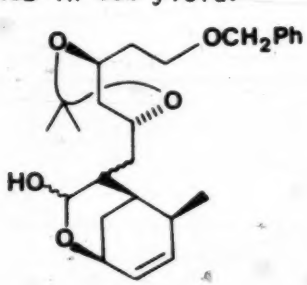
Scheme 20



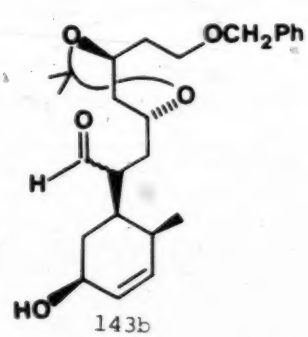
142

This process was carried out in three steps.[65]

Coupled product **140** was reduced with diisobutylaluminum hydride at -78°C to give a mixture of lactol **143a** and hydroxy-aldehyde **143b** in 68% yield.

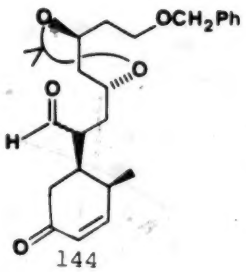


143a



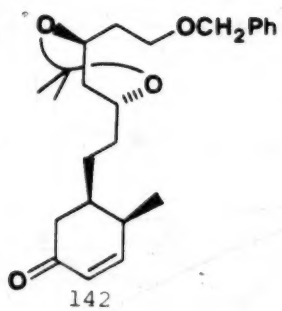
143b

This mixture was oxidized with manganese dioxide in chloroform to give enone aldehyde **144** in 97% yield.



144

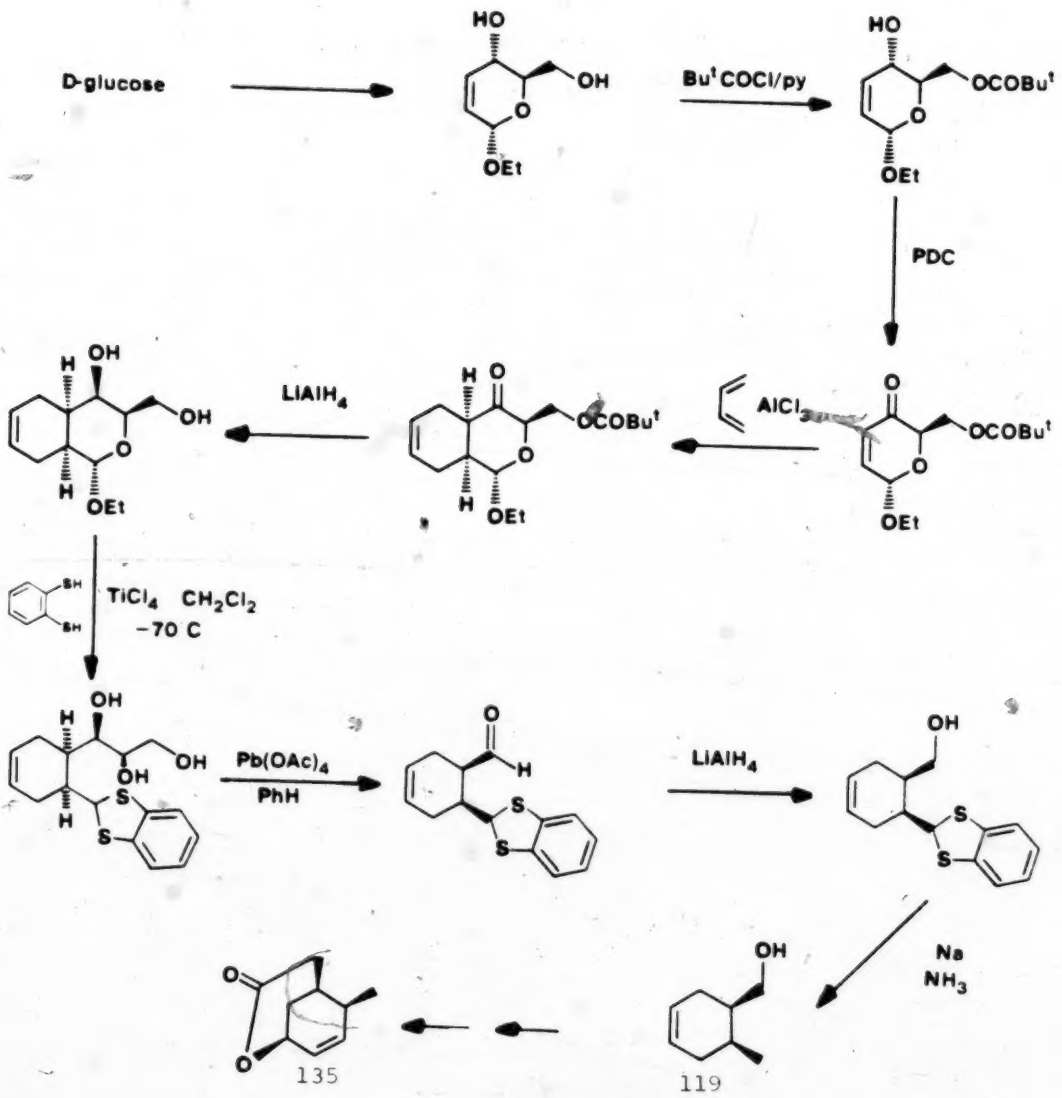
Decarbonylation with Wilkinson's catalyst[66] provided the desired enone **142** in 63% yield.



142

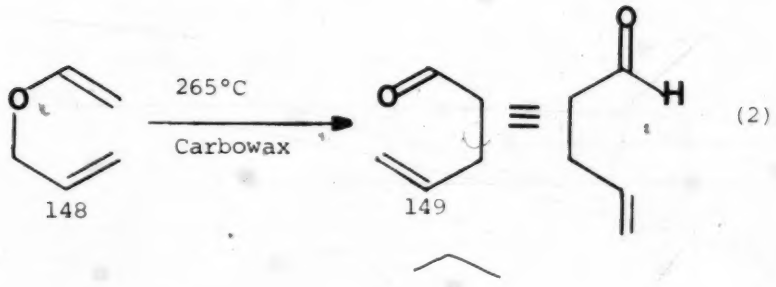
At this point we now possessed the entire carbon skeleton needed for ring B and C and so we turned our attention towards making lactone **135** optically active. Two methods have been developed in our group to do this. The first one involves use of a carbohydrate precursor, namely tri-O-acetyl-D-glucal. The glucal was successfully converted into optically active alcohol **119** in 10 steps[67] as shown in Scheme 21. This sequence was amenable to large scale preparations, but the need for extensive chromatography and some low yielding reactions caused us to seek a simpler route to alcohol **119** and, in

Scheme 21


D-glucose
HO
OH
OEt
Bu^{t}COCl/py
OCOBu^t
PDC
AlCl$_3$
LiAlH$_4$
TiCl$_4$ CH$_2$Cl$_2$
−70 C
Pb(OAc)$_4$
PhH
Na
NH$_3$
135
119

the event, we developed a route based on the use of a chiral oxazolidone.[68] The reaction between acylated oxazolidone **145** (derived from (S)-phenylalanine and crotonyl chloride) and butadiene under Lewis acid catalysis gave a single adduct **146** (62% yield) as shown in Scheme 22. At this point it was a simple matter to obtain the desired optically active alcohol **119** by a series of straightforward reactions (Scheme 22).[69] The optically active alcohol **119** could now be converted into optically active lactone **135** by the route developed with racemic compounds (see Scheme 17).

We now had both synthons for rings B and C optically active and so we turned our attention towards synthesis of the appropriate aldehydes that could be used to make ring A (see Scheme 11). Aldehyde **149** required for the synthesis of compactin can easily be made via Claisen rearrangement of allyl vinyl ether **148** (Equation 2).

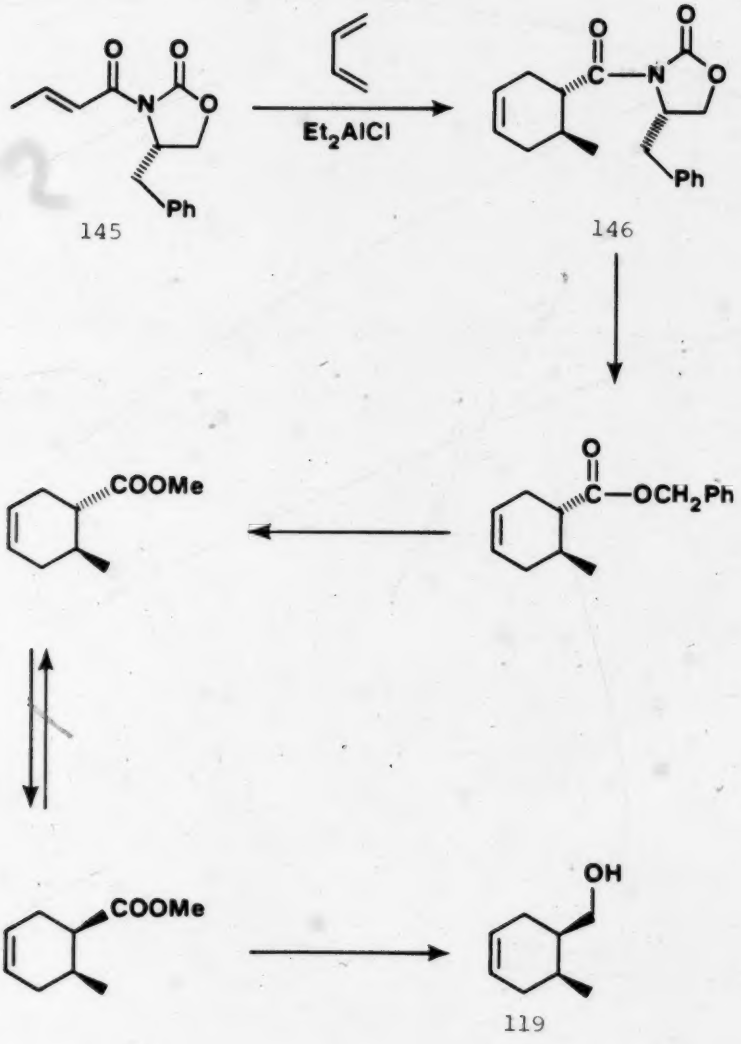


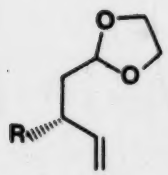
(2)

This reaction can be done on a large scale (50-100g).[70]

The appropriate chiral aldehydes, **150** and **151** for mevinolin and 3 α-ethylcompactin, respectively, could be obtained by two methods.

Scheme 22

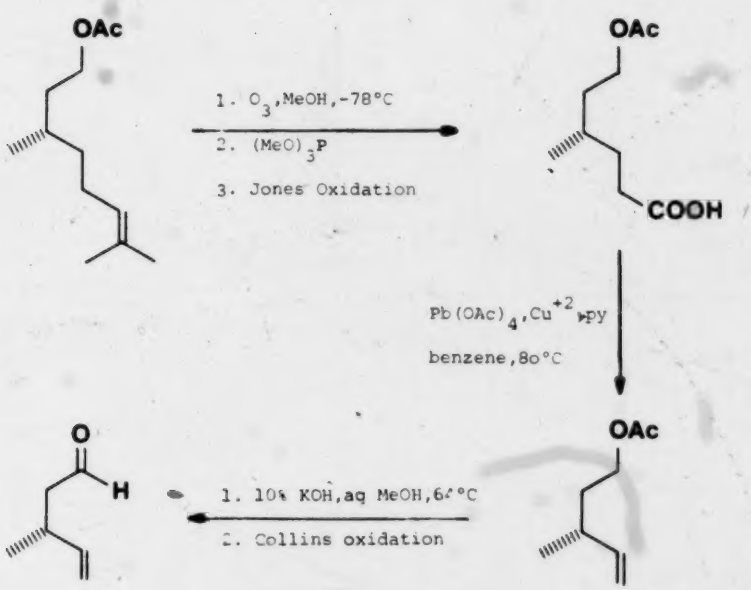




150 R=Me
151 R=Et

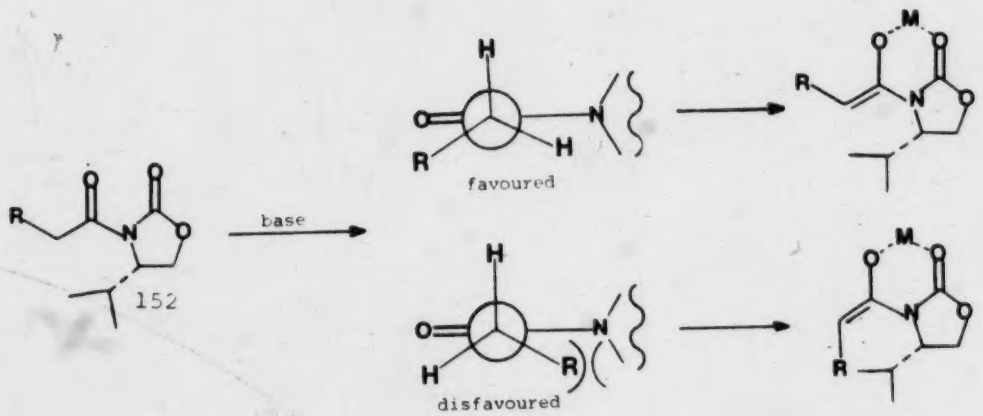
The first one, suitable for mevinolin, would be degradation of a natural product to obtain the desired centre of chirality. The second approach involves asymmetric induction. The first method was used for aldehyde **150** where (S)-citronellol was degraded[71] (Scheme 23).

Scheme 23



The crucial factor in degradation of a natural product is that the natural product be entaniomerically pure. Our starting material contained 10-15%[72] of the other enantiomer. We felt that this was undesirable for our chiral synthesis of mevinolin, and so we turned to the second approach. The method of choice again was the use of chiral oxazolidones[73] which can be alkylated in a highly stereoselective fashion. The high stereoselectivity can be attributed to two factors: upon enolization of compound **152** (Scheme 24), the (Z)-enolate should be the one strongly preferred on the basis of unfavourable interactions in the transition state for formation of the (E)-enolate.[73]

Scheme 24

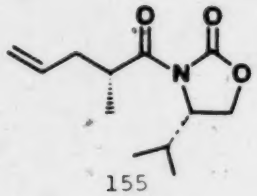


Once the (Z)-enolate is formed the conformation is locked by chelation with the counterion.

The second important factor that controls the stereoselectivity is the high stereofacial bias of the chiral auxiliary causing the electrophile to add only from the si face of the enolate.

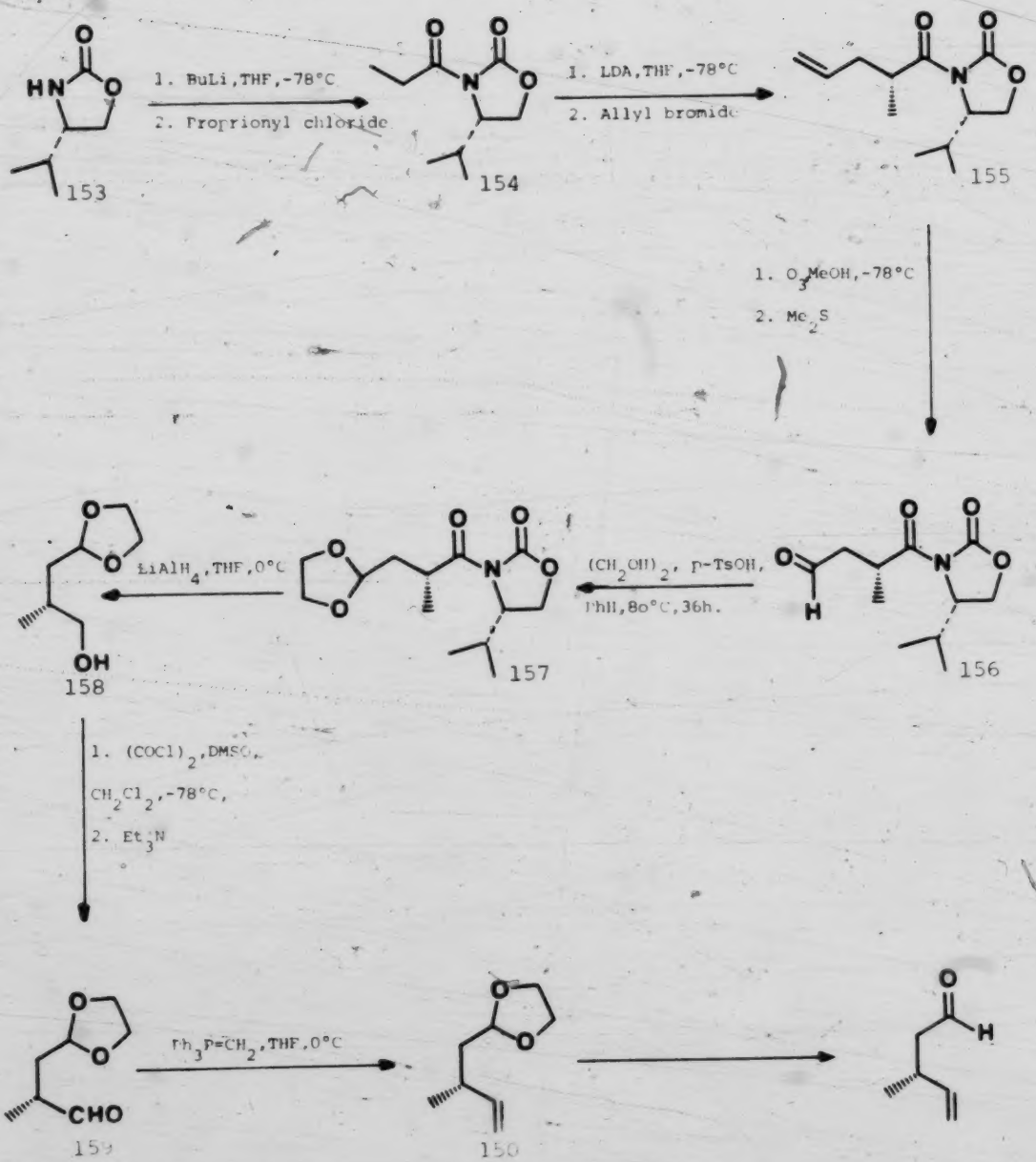
Other advantages of using chiral oxazolidones are that the chiral auxiliary is very easy to remove by transesterification, hydrolysis, or reduction with less than one percent racemization of the induced chiral centre.[73] Also the diastereomers can readily be separated by flash chromatography on a large scale (10-20g).

The chiral auxiliary that we chose was the oxazolidone derived from (S)-valine.[75] (S)-Valine could be readily reduced with lithium aluminum hydride to the amino alcohol[75] and upon reaction with phosgene in aqueous base it gave the required oxazolidone which could be purified easily by recrystalization. Preparation of the chiral acetal **150** was achieved in good yield from chiral oxazolidone **153** (see Scheme 25). Acylated oxazolidone **154** was made in 89% yield from propionyl chloride, and it was then alkylated under literature conditions[73] to give oxazolidone **155** in 73% yield.

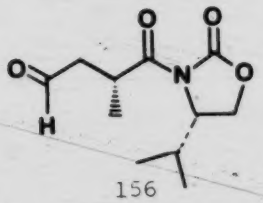


155

Scheme 25

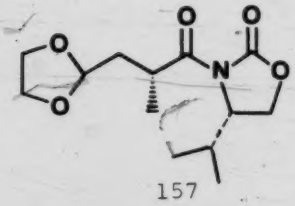

1. BuLi,THF,-78°C
2. Propionyl chloride
1. LDA,THF,-78°C
2. Allyl bromide
153
154
155
1. O3,MeOH,-78°C
2. Me2S
LiAlH4,THF,0°C
(CH2OH)2, p-TsOH,
PhH,80°C,36h.
158
157
156
1. (COCl)2,DMSO,
CH2Cl2,-78°C,
2. Et3N
Ph3P=CH2,THF,0°C
159
150

We chose allyl bromide as our alkylating agent because it gave high selectivity[73] and the double bond present could be cleaved to generate the aldehyde functionality that was required. We found that ozonolysis at -78°C in methanol with a dimethyl sulfide quench gave the required aldehyde **156** in high yields. The aldehyde was not very



156

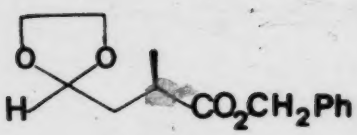
stable at room temperature and so it was protected as its acetal **157.**



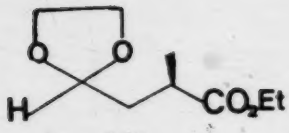
157

Slight racemization occurred during protection of the aldehyde (5%) but the disastereoisomers were easily separated by flash chromatography.

At this point we had at least two options for removal of the chiral auxiliary. Benzyl ester **160** and ethyl ester **161** were both prepared by reaction with the lithium salt of the appropriate alcohol in high yields.

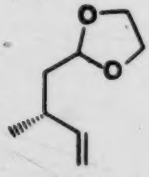


160



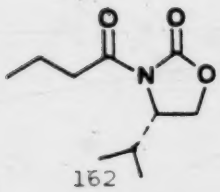
161

In principle the esters could be reduced to the desired aldehyde **159**, but in trial experiments, yields in the reduction were low. The other possibility was to reduce the protected aldehyde **157** with lithium aluminum hydride. The reaction proceeded well at 0°C to give alcohol **158**, but the alcohol could not be obtained totally free of oxazolidone, and so the crude alcohol was oxidized to aldehyde **159** by the method of Swern.[76] The aldehyde was readily purified by flash chromatography, but again it was not stable and so it was converted directly into the desired olefin **150** by a Wittig reaction. The yield was 45% over the three steps from **157**.

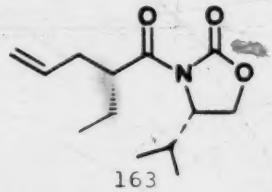


150

The desired acetal **157** for 3 -ethylcompactin could be made by the same route except that we needed an extra carbon. This was furnished by acylation of oxazolidone **153** with butyryl chloride. With the acylated oxazolidone **162** in hand, alkylation[70] with allyl bromide was carried out under similar conditions to those used before to give alkylated product **163** in 79% yield.

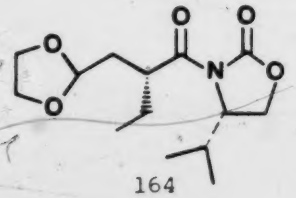


162



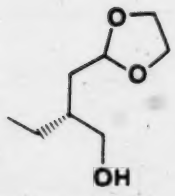
163

Ozonolysis of the double bond and protection of the resulting aldehyde afforded acetal **164** in 68% yield.



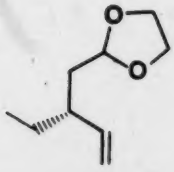
164

The chiral auxiliary was removed as before by lithium aluminum hydride reduction and again the resulting alcohol **165** was difficult to purify. Swern oxidation of the crude alcohol and Wittig olefination



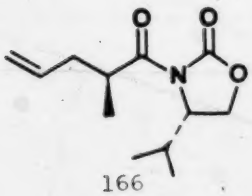
165

gave the olefin **151** in 40% yield over 3 steps from **164.**



151

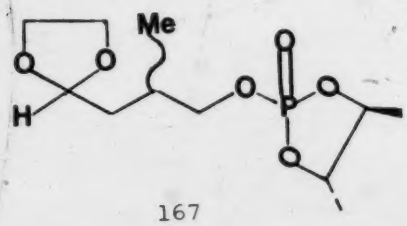
The object of the present synthesis was to prepare aldehydes **150** and **151** in a state of high optical purity. Care was taken to monitor the optical integrity of the intermediates in the synthesis. Alkylated oxazolidone **155** was easily ascertained to be optically pure since isomer **166** which was separated in the preparation of **155**, is readily distinguished from it by ^{1}H NMR measurements.



166

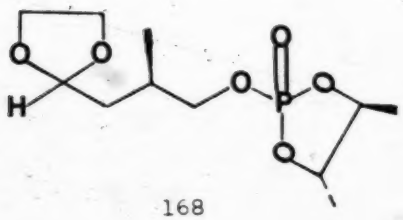
Likewise, **157** is readily shown to be free of its isomer by its 'H NMR spectrum. Reduction to alcohol **158** is not expected to occur with more than 1% racemization on the basis of published work.[74]

We subjected a mixture of **157** and its isomer to lithium aluminum hydride reduction and then examined the ^{31}P NMR spectrum of the derived phosphorous esters **167**.[80]



167

The spectrum showed two peaks with $\Delta\ ^{31}P = 9.6$ Hz. When we subjected alcohol **158** itself to Swern oxidation and then reduction of aldehyde **159**, the ^{31}P NMR spectrum of the derived ester



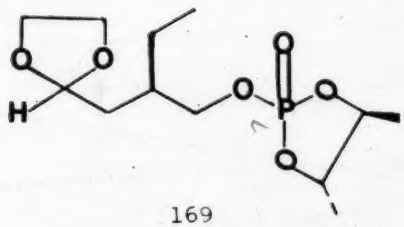
168

168 showed the material to be better than 95% pure.

When **157** was reduced (lithium aluminum hydride), oxidized (Swern), subjected to Wittig reaction (methylene triphenyl phosphine), ozonized, and reduced (lithium aluminum hydride) the resulting alcohol was better than 96.2% pure on the basis of a similar ^{31}P NMR experiment.

We conclude that reduction, Swern oxidation, and Wittig reactions do not alter the stereochemical integrity of the methyl-bearing carbon to any appreciable (i.e., $>5\%$) extent.

When acetal **150** was subjected to ozonolysis, reduction with lithium aluminum hydride and esterification with 2-chloro-4(R), 5(R)-dimethyl-2-oxo-1,3,2-dioxaphospholane, the phosphorus ester **169** was obtained.



169

Examination of the material by ^{31}P NMR showed that some of the undesired isomer was present and work is under way to determine at which stage racemization had occurred.

CONCLUSION

This thesis reports progress made in this laboratory towards the synthesis of mevinolin, compactin, and 3 α-ethylcompactin.

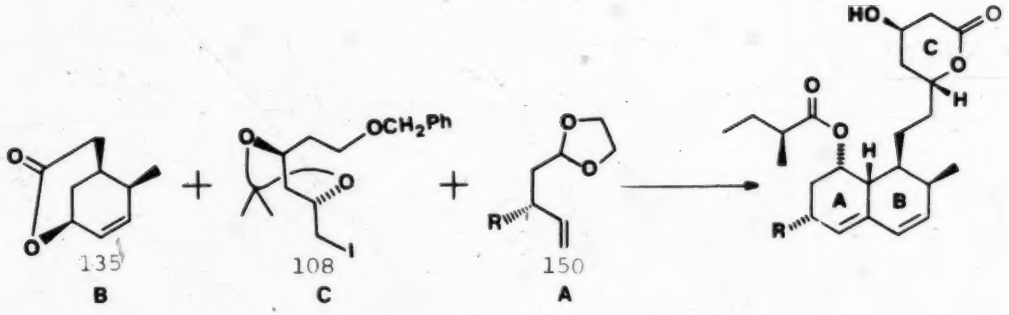
My contribution to this research was:

1) Development of a synthetic route to racemic bicyclic lactone **135**, which is a synthon for ring B of the target molecules. The precise method used was subsequently applied by others in the group to optically pure material.

2) Synthesis in correct optically pure form of precursor **150** to ring A of mevinolin and a synthesis of partially racemized precursor **151** to ring A of 3α-ethylcompactin.

3) Coupling of racemic bicyclic lactone **135** with optically pure iodoketal **108** was repeated by methods previously developed in this laboratory with a view to building up a supply for further work. However, these experiments were not pursued because, in the interim, large quantities of optically pure bicyclic lactone **135** became available and it was decided to confine all work to optically pure materials.

Further work is in progress in the laboratory to use the optically pure fragments **135, 108,** and **150** to assemble mevinolin. 4-Pentenal will be used to make compactin.


OCH2Ph
HO
C
O
H
A
B
R
135
B
108
C
150
A

EXPERIMENTAL

All anhydrous reactions were carried out in the following manner. The reactions were performed in septum-closed flasks under a static pressure of argon and the contents of the flasks were magnetically stirred with dry teflon-coated stirring bars. All apparatus was oven dried (120°C) for at least one hour and cooled in a desicator over Drierite prior to use. Solvents for reactions were dried with the appropriate drying agent under argon and distilled before use. Solvents and liquid reagents were transferred by oven dried syringes. Solids were weighed quickly into oven dried flasks, which were sealed with a septum, and purged with argon. Solvents for chromatography were distilled before use, commercial thin layer chromatography (TLC) plates (silica gel Merck 60 F 2-54) were used and flash chromatography[79] was performed with Merck type 60 (230-400 mesh ASTM) silica gel. TLC plates were visualized using either UV (254nm), iodine, 6N H_2SO_4 in methanol, or phosphomolybdlic acid. All vapour phase chromatographic (VPC) analyses were done on a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector. Prepacked Hewlett-Packard 6 ft. x 1/8 in. O.D. stainless steel analytical columns were used with nitrogen as carrier gas. The columns were 10% w/w Apiezon L, 2% KOH on acid washed chromosorb W (80-100 mesh); QF1 on acid washed dimethyl chlorosilane treated chromosorb W (80-100 mesh); and 10% Carbowax 20M on acid-washed dimethylchlorosilane-treated Chromosorb W (80-100 mesh).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. Liquids and oils were run on sodium chloride plates as neat films. Solids were run as solutions in the appropriate solvent using 0.5mm sodium chloride cells. Only diagnostically important peaks are reported. Melting points (mp) were determined on a Kofler block melting point apparatus and are uncorrected. Boiling points (bp) reported for products distilled in a Kugelrohr apparatus refer to the oven temperature. Proton magnetic resonance (NMR) spectra were recorded with Bruker WP-80 (at 80 MHz), Varian HA-100 (at 100 MHz), Bruker WH-200 (at 200 MHz) or Bruker WH-400 (at 400 MHz) spectrometers, using the appropriate deuterated solvent and tetramethylsilane as internal standard. Carbon-13 nuclear magnetic resonance (^{13}CNMR) spectra were measured with Bruker WP-60 (at 15.08 MHz), Bruker HFX-90 (at 22.6 MHz), Bruker WH-200 (at 50.32 MHz), or Bruker WH-400 (at 100.64 MHz) spectrometers using deuterochloroform as internal standard. Phosphorous-31 NMR (^{31}P NMR) spectra were recorded on a Bruker WH-400 (at 161.98 MHz) using H_3PO_4 as external standard. Abbreviations used for NMR spectra are s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra (MS) were recorded with an A.E.I. model MS50 mass spectrometer. Microanalyses were performed by the microanalytical laboratory of this department. Spinning band distillations were performed using Perkin Elmer 151 or 251 annular stills. Optical rotations were measured on a Perkin Elmer 141 polarimeter using a 1 dm cell.

Materials

Dry benzene, ether, and tetrahydrofuran (THF) were distilled before use from sodium benzophenone ketyl. Dry diisopropylamine, triethylamine, chloroform, dichloromethane, pyridine, and toluene were distilled from calcium hydride. Dry dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and 1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H) pyrimidone (DMPU) were distilled from calcium hydride under reduced pressure and stored over molecular sieves (3A). Commercial (Aldrich) solutions of n-butyl lithium in hexane were titrated before use using 2,5-dimethoxybenzyl alcohol as indicator.[78] Butyryl chloride (Aldrich), allyl bromide (Aldrich), and propionyl chloride (Aldrich) were distilled before use. All other reagents were used as received.

(±) cis-6-Methyl-3 cyclohexene-1-methanol (119).[54]

Ester **96**[52,53] (3.000 g, 19.45 mmol) in dry THF (30 mL) was added dropwise to a magnetically stirred and cooled (ice bath) suspension of lithium aluminum hydride (758.4 mg, 20.0 mmol) in dry THF (30 mL). After the addition the mixture was refluxed for 24 h and then cooled to 0°C and hydrolized by dropwise addition (stirring) of water (3 mL), 10% w/v aqueous sodium hydroxide (3 mL), and water (3 mL). The resulting precipitate was filtered off using a sinter and washed thoroughly with ether. The combined ether solutions were dried ($MgSO_4$) and evaporated. Kugelrohr distillation (102°C, 15 mm), of the residual oil gave **119** (2.4g, 97%) as a colorless oil of greater than 95% purity (VPC, Apiezon, 150°C): NMR ($CDCl_3$, 200 MHz) δ 5.63 (m, 2H), 3.57 (m, 2H), 2.32-1.66 (m, 6H), 1.29 (br s, 1H), 0.91 (d, 3H, J=1Hz);

^{13}C ($CDCl_3$, 50.32 MHz): δ 125.4(d), 125.0(d), 63.9(t), 39.3(d), 32.4(t), 27.4(d), 25.2(t), 24.1(q); IR (film) 3650-3100, 1650 cm^{-1}; exact mass, m/e 126.1043 calcd for $C_8H_{14}O$, m/e 126.10447. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C,76.11; H, 11.20.

(±)-cis-6-Methyl-4-methylbenzene sulfonate-3-cyclohexene-1- methanol (131).

Dry dichloromethane (250 mL) and dry pyridine (37.6 mL, 465 mmol) were added to **119** (19.517g, 155 mmol) and the mixture was stirred magnetically with protection from moisture and cooled in an ice bath. p-toluenesulfonyl chloride (30.5g, 160 mmol) was added followed by 4-dimethylaminopyridine (DMAP) (500 mg). The ice bath was removed and stirring was continued for 48 h (TLC control, silica, 3:7 ethylacetate-hexane) and then the mixture was acidified to pH 2 at ice bath temperature by slow addition of conc. HCl (stirring). The reaction mixture was extracted with dichloromethane (2x50 mL) and the organic extract was washed with aqueous saturated sodium bicarbonate solution (2x50 mL) and then brine (1x50 mL). The organic extract was dried ($MgSO_4$) and evaporated. The crystalline residue was kept (ca 1h) under oil pump vacuum. The product was dissolved in hot hexane and the solution was allowed to cool, first to room temperature and then to 0°C to afford **131** (37.09g, 85%) as a white crystalline compound. In this experiment the mother liquors were not examined further: mp 41-43°C NMR ($CDCl_3$, 200 MHz), δ 7.80 (d, 2H, J=8Hz), 7.35 (d, 2H, J=8Hz), 5.55 (br s, 2H), 3.90 (m, 2H), 2.42 (s, 3H), 2.15-1.60 (m, 6H), 0.78 (d, 3H, J=8Hz); ^{13}C ($CDCl_3$, 22.63 MHz): δ 144.61, (s), 133.09 (s), 129.73 (d), 127.78 (d), 125.56 (d), 124.13 (d), 71.75 (t),

36.26 (d), 31.84 (t), 27.29(d), 24.94 (t), 21.57 (q), 14.47 (q); IR ($CHCl_3$): 1650, 1600, 1357, 960 cm^{-1}; exact mass, m/e 280.1142 (calcd for $C_{15}H_{20}SO_3$ 280.3886). Anal. Calcd for $C_{15}H_{20}SO_3$: C, 64.28; H, 7.14. Found: C,64.28, H, 7.16.

(±)-cis-6-Methyl-3-cyclohexene-1-acetonitrile (132).

A solution of **131** (3.0714 g, 10.95 mmol) in reagent DMSO (4 mL) was added dropwise by syringe to a preheated (80°C) solution (6 mL) of sodium cyanide (646 mg, 13.18 mmol) in DMSO. The mixture was stirred at 80°C for 48h with protection from moisture, TLC control (silica, 1:5 ethylacetate-hexane), cooled to room temperature and diluted with water (50 mL). The mixture was extracted with ethyl acetate (5x50 mL) and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Distillation of the residue gave **132** (1.2619 g, 85%) as a colorless oil of greater than 95% purity (VPC, QF-1, 80°C): bp 38-41°C (0.1 mm); NMR ($CDCl_3$, 400 MHz): δ 5.65 (S, 2H), 2.40-1.90 (m, 7H), 1.85 (m, 1H), 0.89 (d, 3H, J=8Hz). ^{13}C ($CDCl_3$, 100.02): δ 125.40 (d), 123.79 (d), 119.04 (s), 34.35 (d), 31.12 (t), 29.44 (d), 28.20 (t), 18.51 (t), 14.87 (q); IR (film) 2250 cm^{-1}; exact mass m/e 135.1052 (calcd for $C_9H_{13}N$ 135.2103); Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 80.05; H, 9.64.

(±)-cis-6-Methyl-3-cyclohexene-1-acetic acid (133).

The nitrile **132** (1.2619 g, 9.41 mmol) was added to a solution (60 mL) of sodium hydroxide (1.882, 47.05 mmol) in water. The resulting mixture was refluxed for 12 h, cooled and acidified to pH 2 with ice bath cooling by addition of 6 N HCl. The solution was

extracted with ether (3x30 mL) and the combined extracts were washed with brine (1x40 mL), dried ($MgSO_4$), and evaporated. Kugelrohr distillation of the residue gave **133** (1.350 g, 93%) as a homogeneous (silica, 2:5 ethylacetate-hexane) oil: bp 134-135 (0.22 mm); NMR ($CDCl_3$, 400 MHz): δ 12.4 (br, 1H), 5.60 (s, 2H), 2.40-2.10 (m, 5H), 2.00-1.80 (m, 2H), 1.79 (m, 1H), 0.90 (d, 3H, J=8Hz); ^{13}CNMR ($CDCl_3$, 100.62 MHz): δ 178.94 (s), 125.65 (d), 124.95 (d), 35.72 (t), 33.80 (d), 31.92 (t), 30.19 (d), 28.85 (t), 15.32 (q); IR (film): 3500-2500, 1705, 1650 cm^{-1}; exact mass, m/e 154.0999 (calcd for $C_9H_{14}O_2$ 154.2104). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15, Found: C, 69.92; H, 9.20.

(+)-2-endo-4-exo-4-Iodo-2-methyl-6-oxabicyclo[3.3.1]non-7-ene (134).

Acid **133** (15.31 g, 99 mmol) was stirred with water (300 mL) and solid sodium bicarbonate (20 g, 238 mmol) was added in portions. A solution of iodine (50.25 g, 198 mmol) and potassium iodide (80 g, 480 mmol) in water (500 mL) was added dropwise with stirring and the mixture was stirred in the dark for 85 h (TLC control silica, 1:4 ethyl acetate-hexane). The mixture was then diluted with dichloromethane (100 mL) and solid sodium thiosulfate was added in portions with vigorous stirring until the iodine colour was discharged. The organic layer was separated and the aqueous phase was extracted with more dichloromethane (3x100 mL). The combined organic extracts were washed with 5% w/v aqueous sodium hydrogen sulfite and dried ($MgSO_4$). Evaporation of the solvent gave off-white crystals which were recrystallized from ethanol to afford **134** (22.08 g, 79%) as a homogeneous (TLC, silica,

1:4 ethylacetate-hexane) material: mp 97-98°C; NMR ($CDCl_3$, 400 MHz): δ 4.80 (s, 1H), 4.65 (s, 1H), 2.75 (d, 1H, J=6Hz), 2.65 (d, 2H, J=4Hz), 2.60 (m, 1H), 2.30 (m, 1H), 2.10 (m, 2H), 1.90 (d, 1H, J=8Hz), 1.00 (d, 3H, J=8Hz); ^{13}CNMR ($CDCl_3$, 50.32 MHz): δ 170.32 (s), 77.75 (d), 33.88 (t), 31.57 (d), 30.61 (t), 30.02 (d), 27.62 (d), 18.70 (q); IR (CCl_4): 1735 cm^{-1}; exact mass (No M+), m/e 153.0911 (calcd for $C_9H_{13}O_2$ (M-I) 153.0914); Anal. Calcd for $C_9H_{13}IO_2$: C, 38.59; H, 4.68, Found: C, 38.56, H, 4.73.

(±)-endo-2-Methyl-6-oxabicyclo[3.3.1]non-3-ene-7-one (135).

1,5-Diazabicyclo[4.3.0]non-5-ene (5.530 g, 44.51 mmol) was added to a solution of **134** (4.15 g, 14.8 mmol) in dry toluene (35 mL) and the mixture was refluxed for 5h under argon (TLC, silica, 1:1 ethylacetate-hexane), cooled, and diluted with ether (300 mL). The solution was shaken with ice-cold 2N HCl (70 mL), then with an aqueous solution containing sodium thiosulfate (20% w/v) and sodium bicarbonate (5% w/v), and it was then dried ($MgSO_4$) and evaporated to afford a mass of white crystals. These were recrystallized from ether to afford **135** (1.960 g, 87%) as a pure (TLC, silica, 1:1 ethylacetate hexane) material: mp 60-61°C; NMR ($CDCl_3$, 400 MHz): δ 6.00 (m, 1H), 5.82 (m, 1H), 4.76 (m, 1H), 2.60 (m, 3H), 2.30 (m, 2H), 2.00 (m, 1H), 1.1 (d, 3H, J=8Hz); ^{13}CNMR ($CDCl_3$, 100.62), δ 176.96 (s), 136.16 (d), 125.43 (d), 69.92 (d), 35.47 (d), 30.32 (t), 30.13 (d), 29.89 (t), 17.81 (q); IR (CCl_4): 1725, 1645 cm^{-1}; exact mass: 152.0836 (calc for $C_9H_{12}O_2$ 152.2044); Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95, Found: C, 71.10; H, 8.02.

(S)-Diethyl malate (136)[57]

(S)-Malic acid (100 g, 746 mmol), absolute ethanol (250 mL) and chloroform (300 mL) were combined and ion exchange resin (30.0 g, C-250, Baker; freshly charged by passing 5% HCl through followed by water) was added. The solution was refluxed using a Dean-Stark apparatus for 36 h and then using a Soxhlet apparatus filled with molecular sieves (4A) for 24 h. The reaction mixture was filtered and the solvent was evaporated. The residue was distilled to give **136** (133 g, 95%): bp 68-70°C (0.25 mm) (lit:[57] 85-86°C (0.5 mm) $[\alpha]_D^{25}$ - 11.03 neat; (lit $[\alpha]_D^{20}$ -10.18 (neat);[57] NMR ($CDCl_3$, 400 MHz): δ 4.48 (dd, 1H, J=6Hz, J=1.5Hz), 4.25 (dq, 2H, J=3Hz, J=6Hz), 4.15 (q, 2H, J=6Hz), 3.20 (br, 1H), 2.80 (ddd, 2H, J=8Hz, J=4Hz), 1.30 (m, 6H).

(S)-1,2,4-Butanetriol (137)[58]

(S)-Diethyl malate **136** (60.0 g, 320 mmol) in ether (60 mL) was added slowly to a cooled (0°C) suspension of lithium aluminum hydride (25 g, 660 mmol) in ether (700 mL). The reaction mixture was refluxed overnight and then cooled to 0°C. Celite (50g) and anhydrous sodium sulfate (20g) were added. The reaction mixture was carefully diluted with water (30 mL), 10% (w/v) aqueous sodium hydroxide (30 mL), and water (70 mL). The white precipitate was filtered and washed well with ether and the filtrate was discarded. The dry white solid was then washed well with ethanol (800 mL) and the filtrate was evaporated. Distillation of the residue gave **137** (17.38 g, 51%): bp 125-126°C (0.1 mm) (lit bp[58] 121-123°C (0.03mm)).

(S)-2,2-Dimethyl-1,3-dioxolane-4-ethanol (103)[60]

Triol **137** (34.0 g, 320 mmol) was dissolved in dry acetone (1.5 L) and p-toluenesulfonic acid (1.5 g) was added. The reaction mixture was stirred at room temperature for 2h and 4A molecular sieves (ca 1.0 g) were then added. Stirring was continued overnight. Solid sodium bicarbonate (2.0 g) was added, and the mixture was stirred for a further 45 min. Solids were removed by filtration and the solvent was evaporated. The residue was distilled to give **103** (40.0 g, 86%): bp 55-60°C (0.3 mm); $[\alpha]_D^{26}$ +1.30 (neat), (lit[60] $[\alpha]_D$ 2.23° (9.8 MeOH); NMR ($CDCl_3$, 200 MHz): δ 4.30 (m, 1H), 4.12 (dd, 1H, J=2Hz, J=6Hz), 3.79 (m, 2H), 3.60 (m, 1H), 3.16 (t, 1H, J=6Hz), 1.85 (dt, 2H, J=3Hz, J=4Hz), 1.46 (s, 3H), 1.40 (s, 3H). The material is known to contain 10% of 2,2 Dimethyl-1,3-dioxane-4-ethanol.[60]

(S)-2,2-Dimethyl-4-2-(phenylmethoxy) ethyl)-1,3-dioxolane (138).

The alcohol **103** (37.2 g, 265 mmol) in dimethylformamide (40 mL) was added to a cooled (0°C) suspension of sodium hydride (7.64 g, 33% w/v, 320 mmol) in dimethylformamide (350 mL) and the mixture was then stirred at room temperature for 1h. The solution was cooled to 0°C and benzyl bromide (38.2 ml, 320 mmol) was added. Stirring was continued for 20h at room temperature and then cooled (0°C) and diluted with water (100 mL). The resulting solution was allowed to warm to room temperature and it was then extracted with ethyl acetate (400 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The resulting oil was distilled to give **138** (51.5 g, 91%): bp 104-106°C (0.45 mm); $[\alpha]_D^{25.5}$ -8.60° (neat); NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 5H), 4.50 (s, 2H), 4.20 (m, 1H), 4.05

(dd, 1H, J=6Hz, J=8Hz), 3.56 (m, 2H), 1.88 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H); IR (film) 1468, 1095 cm^{-1}.

(S)-4-(Phenylmethoxy)-1,2-butandiol (104).[61]

The fully protected triol **138** (14.2 g, 600 mmol) was dissolved in acetic acid (75% v/v, 48 mL) and the solution was stirred at 50°C for 1 h. It was cooled to 0°C and carefully neutralized with saturated aqueous potassium carbonate (60 mL). The mixture was extracted with ethyl acetate (150 mL) and the organic phase was washed with brine (60 mL), dried ($MgSO_4$), and concentrated. The crude product was distilled to give **104** (10.7 g, 90%): bp 130-135°C (0.1 mm) $[\alpha]_D^{25.5}$ -20.7 (1.20M, EtOH), (Lit.[54] $[\alpha]_D^{27}$ -15.69 (0.3M, MeOH)); NMR ($CDCl_3$, 200 MHz): δ 7.30 (m, 5H), 4.54 (s, 2H), 3.90 (m, 1H), 3.70 (m, 2H), 3.50 (m, 2H), 3.40 (br, 1H), 2.80 (br, 1H), 1.80 (m, 2H); IR (film): 3400, 1495, 1451, 1095 cm^{-1}.

(S)-(2-(Phenylmethoxy)-ethyl)oxitane (105).

The diol **104** (3.2 g, 16.3 mmol) was dissolved in dichloromethane (60 mL), and pyridine (2 mL) was injected. The solution was cooled (-60°C) and freshly distilled methanesulfonyl chloride (1.6 mL, 20.4 mmol) was added. The solution was stirred at -60°C for 2 h, the cold bath removed, and stirring was continued for 20 h. Water (10 ml) was added and the solution was acidified with 2 N HCl, and extracted with dichloromethane (2x40 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (60 mL) and brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the crude mesylate which was dissolved in ether (40 mL). N-Benzyltrimethyl ammonium hydroxide (8 mL, 40% in methanol) was added and the solution

was stirred for 1.25 h and the white precipitate was filtered off. The filtrate was washed successively with 2 N HCl (10 mL) and brine (20 mL), and dried ($MgSO_4$). Evaporation of the solvent and chromatography over silica gel (3x20 cm; 1:1 ethyl acetate-hexane) followed by distillation to give **105** (1.9 g, 65%) from diol **104**: bp 70-72°C (0.1 mm); $[\alpha]_D^{26}$ -13.4° (.39M, MeOH); NMR ($CDCl_3$, 400 MHz): δ 7.50 (m, 5H), 4.54 (s, 2H), 3.62 (m, 2H), 3.06 (m, 1H), 2.77 (dd, 1H, J=4.4Hz, J=5.5Hz), 2.50 (dd, 1H, J=2.3Hz, J=5Hz), 1.85 (m, 2H); ^{13}CNMR ($CDCl_3$, 22.63 MHz): δ 138.37, 128.37, 127.58, 73.05, 67.01, 47.98, 46.94, 32.97; IR (film): 1365, 1105, 745, 705 cm^{-1}; exact mass m/e 178.0988 (Calcd for $C_{11}H_{14}O_2$ 178.2334); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86, Found: C, 73.90; H, 7.92.

(S)-1-(Phenylmethoxy)-5-hexen-3-ol (106).

Epoxide **105** (2.8 g, 15.7 mmol) was dissolved in THF (100 mL) and cooled to 0°C. Vinyl magnesium bromide (46 mL, 1M in THF) was added dropwise and the mixture was stirred for 2 h at 0°C. Water (20 mL) was added to generate a white precipitate which was dissolved by addition of 6 N HCl (10 mL). The solution was extracted with ether (2x100 mL) and the combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$), and concentrated. The residue was distilled to give **106** (3.2 g, 995 mmol): bp 115-116°C (0.4 mm); $[\alpha]_D^{26}$ -4.6 (1.13 M, CCl_4); NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 5H), 5.85 (m, 1H), 5.13 (m, 2H), 4.53 (s, 2H), 2.28 (dd, 2H, J=3.5Hz), 1.80 (m, 2H); ^{13}CNMR ($CDCl_3$, 15.08 MHz): δ 138.15, 134.99, 128.54, 127.80, 117.63, 73.39, 70.35, 68.95, 41.99, 36.02; IR (film): 3440,

1640, 1100 cm^{-1}; exact mass m/e 206.1307 (calcd for $C_{13}H_{18}O_2$ 206.2873).

(4-S-cis)-4-(Iodomethyl)-6-(2-phenylmethoxyethyl)-1,3-dioxan-2-one (107).

n-Butyllithium (8.8 mL, 1.60 M in Hexane) was added to a cooled (0°C) solution of alcohol **106** (2.90 g, 14.1 mmol) in THF (100 mL) and the mixture was stirred for 10 minutes at 0°C. The solution was warmed to room temperature and carbon dioxide was bubbled into it for 30 min. The reaction mixture was again cooled to 0°C, and a solution of iodine (11.4 g, 44 mmol) in THF (30 mL) was added dropwise. The solution was stirred at 0°C for 2 h and then for 30 min after the cold bath had been removed. The reaction mixture was diluted with ethyl acetate (250 mL) and the organic layer was washed with a solution containing 20% w/v sodium thiosulfate and 5% w/v sodium bicarbonate (100 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (3x10 cm; 1:1 ethyl acetate hexane) to afford **107** (3.67 g, 69%) as a 9:1 erythro:threo mixture: NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 5H), 4.70 (m, 1H), 4.49 (dd, 2H, J=11.5Hz, J=20Hz), 4.40 (m, 1H), 3.64 (m, 2H), 3.35 (dd, 1H, J=11Hz, J=4.2 Hz), 3.23 (dd, 1H, J=11Hz, J=7.5Hz), 2.42 (ddd, 1H, J=14.5Hz, J=3Hz), 1.98 (m, 2H), 1.72 (ddd, 1H, J=14.5Hz, J=11.5Hz); ^{13}CNMR ($CDCl_3$, 22.5 MHz): δ 148.26, 138.04, 128.55, 127.80, 77.27, 75.86, 73.38, 65.01, 35.43, 33.56, 5.27; IR (film): 1740 cm^{-1}; exact mass m/e 376.0172 (calcd for $C_{14}H_{17}IO_4$ 376.1933).

(4-S-cis)-2,2-Dimethyl-4-(iodomethyl)-6-(2-(phenylmethoxy) ethyl)-1,3- dioxane (108).

The iodocarbonate **107** was dissolved in dry acetone (50 ml) and p-toluenesulfonic acid monohydrate (250 mg, 1.3 mmol) was added. The solution was refluxed for 4 h, cooled, and stirred for another 12 h at room temperature. Sodium bicarbonate (1.0 g) was added and the mixture was stirred briefly and then filtered. The acetone was evaporated and the residue was dissolved in ether (30 mL) and washed with a solution of 20% w/v sodium thiosulfate and 5% w/v sodium bicarbonate (10 mL), and dried ($MgSO_4$). Evaporation of the solvent, chromatography of the residue over silica gel (3x15 cm, 1:4 ethylacetate-hexane), and distillation gave **108** (1.90 g, 63%): bp 150-155°C (0.2 mm); $[\alpha]_D^{26}$ +7.2 (2.1 m, CH_2Cl_2); NMR ($CDCl_3$, 400 MHz): δ 7.32 (m, 5H), 4.50 (two d, 2H, J=12Hz), 4.06 (m, 1H), 3.84 (m, 1H), 3.54 (m, 2H), 3.10 (two dddd, 2H, J=10Hz, J=6Hz), 1.75 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.12 (ddd, 1H, J=11Hz, J=12Hz); ^{13}CNMR ($CDCl_3$, 50.32 MHz): δ 138.45, 128.30, 127.56, 127.51, 99.24, 69.16, 65.99, 65.90, 36.78, 36.34, 29.91, 19.88, 9.50; IR (film): 1380, 1200, 1165, 1095 cm^{-1}; exact mass m/e 390.0675 (calcd for $C_{16}H_{23}IO_3$ 390.2635); Anal. Calcd for $C_{16}H_{23}IO_3$: C, 49.24; H, 5.90, Found: C, 49.36; H, 5.85.

(2'R, 4'S, 2-endo)-2',4'-O-Isopropylidene-8-(2',4'-dihydroxy-6'-(phenylmethoxy) hexyl)-2-methyl-6-oxabicyclo(3.3.1)non-3-ene-7-one (140).

n-Butyllithium (1.66 mL, 1.20 M in hexane) was added to a cold solution (-78°C) of diisopropylamine (.280 mL, 2 mmol) in THF (4 mL)

under argon. The cold bath was removed and the mixture was stirred for 20 min. The solution was recooled to -78°C and lactone **135** (152 mg, 1 mmol) in THF (1 mL + 0.5 mL rinse) was added dropwise. Stirring was continued for 1.25 h and iodide **108** (390 mg, 1 mmol) in THF (1 mL + 0.5 mL rinse) was added to the enolate solution in one portion. 1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidone (DMPU) (1.6 mL) was added immediately. The mixture was stirred at -78°C for 1 h, the cold bath was removed, and stirring at room temperature was continued for 36 h. Saturated aqueous ammonium chloride (1 mL) was added and the phases were separated. The organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting yellow oil was chromatographed over silica gel (20x2 cm; 1:3 ethyl acetate-hexane) to give **140** ((268 mg, 65%), 75% based on recovered lactone **135** (216 mg)). The material was homogeneous by TLC (silica, 1:3 ethylacetate-hexane); NMR ($CDCl_3$, 400 MHz): δ 7.35 (m, 5H), 5.95 (m, 1H), 5.72 (m, 1H), 4.73 (m, 1H), 4.52 (m, 2H), 4.19 (m, 1H), 4.05 (m, 1H), 3.58 (m, 2H), 2.70 (m, 1H), 2.52 (m, 1H), 1.40 (m, 6H), 1.11 (m, 3H), 1.00-2.35 (complex system, 9H); IR (film): 1725 cm^{-1}; exact mass (No M+), m/e 399.2167 (calcd for $C_{24}H_{31}O_6$ ($M-CH_3$) 399.5119.

(2'R, 4'S, 2-endo)-2',4'-O-Isopropylidene-8-(2',4'-dihydroxy-6'-(phenylmethoxy) hexyl)-2-methyl-6-oxabicyclo (3.3.1)-non-3-ene-7-ol (143).

Diisobutylaluminum hydride (1 mL, 1M in CH_2Cl_2) was added dropwise to lactone **140** (200 mg, .48 mmol) in dichloromethane (5 mL) at -78°C, and the mixture was stirred for 1.5 h. Saturated aqueous ammonium chloride (1 ml) was added dropwise to the cold solution and

the mixture was diluted with dichloromethane (30 mL). The mixture was washed with water (10 mL), dried ($MgSO_4$) and concentrated. The crude product was chromatographed over silica gel (2x17 cm; 1:3 ethyl acetate-hexane) to give **143a** in equilibrium with its open form **143b** (137 mg, 68%) and starting material **140** (46 mg). The reaction product (**143a** and **143b**) was homogeneous by TLC (silica, 1:3 ethyl acetate-hexane): NMR ($CDCl_3$, 400 MHz): δ 9.48 (d, 0.15H, J=4Hz), 7.35 (m, 5H), 5.82 (m, 1H), 5.74 (m, 1H), 5.40 (d, 1H, J=6Hz), 5.13 (m, 1H), 4.50 (m, 2H), 4.30 (m, 1H), 4.08 (m, 1H), 3.86 (m, 1H), 3.55 (m, 2H), 2.50 (m, 1H), 1.2-2.40 (m, 10H), 1.45 (s, 3H), 1.40 (s, 3H), 1.10 (s, 3H), 0.90 (m, 3H); IR (film): 3410, 1720 cm^{-1}; exact mass (No M+), m/e 398.2458 (calcd for $C_{25}H_{34}O_4$ (M+-18) 398.5471).

(3'R,5'S,(cis)-3',5'-O-Isopropylidene-5-(1'-formyl-3',5'-dihydroxy-7'-(phenylmethoxy) heptyl)-4-methylcyclohex-2-en-1-one (144).

Lactol **143** (980 mg, 23 mmol) was dissolved in dry choloroform (32 mL) and sodium bicarbonate (300 mg) and manganese dioxide (3.50 g) were added. The mixture was stirred vigorously for 48 h at room temperature and more manganese dioxide (1.15 g) and sodium bicarbonate (100 mg) were added. After a further 16 h of stirring the reaction was complete (TLC control, silica, 1:1 ethylacetate-hexane). The mixture was filtered through Celite and the solvent was evaporated to give pure aldehyde **144** (950 mg, 97%) which was homogeneous by TLC (Silica, 1:1, ethylacetate-hexane). NMR ($CDCl_3$, 400 MHz): δ 9.58 and 9.42 (two d, 1H, J=4Hz), 7.32 (m, 5H), 7.02 (dd, 1H), 5.98 (d, 1H, J=10Hz), 4.50 (m, 2H), 4.04 (m, 1H), 3.80 (m, 1H), 3.58 (m, 2H), 2.38

(m, 2H), 1.75 (m, 3H), 1.65-1.20 (m, 2H), 1.48 (m, 6H), 1.10 (m, 3H); IR (CCl_4): 1760, 1730, 1678 cm^{-1}; exact mass (No M^+) m/e 399.2501; (calcd for $C_{24}H_{31}O_5$ (M^+-15) 399.5127).

(3'R, 5'S, cis)-3',5'-O-Isopropylidene-5-(3',5'-dihydroxy-7'-(phenylmethoxy) heptyl)-4-methyl cyclohex-2-en-1-one (142).

Enone-aldehyde **144** (102 mg, 0.25 mmol) was dissolved in dry benzene (5 mL) and Wilkinson's catalyst (240 mg, 0.26 mmol) was added. The solution was refluxed under argon for 20 h and was then cooled to room temperature. The benzene was evaporated and the residue was chromatographed over silica gel (1.5x12 cm; 1:4 ethyl acetate-hexane) to give **142** (60 mg, 63%), which was homogeneous by TLC (silica, 1:4 ethylacetate-hexane): NMR ($CDCl_3$, 400 MHz): δ7.30 (m, 5H), 6.95 (m, 1H), 5.94 (d, 1H, J=12Hz), 4.50 (m, 2H), 4.04 (m, 1H), 3.78 (m, 1H), 3.55 (m, 2H), 2.60-2.10 (m, 4H), 1.78 (m, 2H), 1.45 (m, 1H), 1.40 (m, 6H), 1.60-1.20 (m, 4H), 1.15 (m, 1H), 1.04 (m, 3H); IR (film): 1675 cm^{-1}; exact mass (No M^+) 371.2227 (calcd for $C_{23}H_{31}O_4$ (M^+-15) 371.8607).

(S)-4-(1-Methylethyl)-2-oxazolidone (153).[73,74,75]

A suspension of lithium aluminum hydride (27 g, 711 mmol) in THF (800 mL) was stirred vigorously at 0°C with a mechanical stirrer and a slurry of (S)-valine (50 g, 427 mmol) in THF (500 mL), was added slowly. The ice bath was removed, the solution allowed to warm to room temperature over 30 min, and the mixture was refluxed overnight. The reaction mixture was recooled to 0°C and Celite (29 g) was added. Water (29 mL) was carefully added dropwise followed by 10% (w/v) aqueous sodium hydroxide (29 mL) and water (70 mL). The resulting

white precipitate was filtered through a pad of Celite and the insoluable material was washed thoroughly with ethyl acetate (ca. 300 mL). The filtrate was washed with 10% (w/v) aqueous sodium hydroxide (2x100 mL), brine (100 mL), and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was distilled to afford (S)-valinol[75] (45.58 g, 94%): bp, 53-54°C (0.5 mm) which was dissolved in toluene (350 mL) and cooled to 0°C. Aqueous potassium hydroxide 12.5% w/v (470 mL) was added to the solution of (S) valinol. The two-phase mixture was stirred vigorously at 0°C with a mechanical stirrer and a solution of phosgene (79 g) in toluene (200 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight to allow excess of phosgene to evaporate into the fumehood. The reaction mixture was transferred to a separatory funnel and the aqueous phase was washed with toluene (3x100 mL). The combined toluene solutions were dried ($MgSO_4$) and concentrated to afford a yellow solid. Recrystallization from ethyl acetate and hexane gave white needles of **153** (24.36 g, 45% from (S)-valine): mp 70-72°C (lit.[74] 71-72°C) $[\alpha]_D^{25}$ +15.1° (7.0, $CHCl_3$) (lit.[74] $[\alpha]_D$ +14.8° (7.0, $CHCl_3$)); NMR ($CDCl_3$, 200 MHz): δ 6.4 (br, 1H), 4.46 (dd, 1H, J=10Hz, J=8Hz), 4.13 (dd, 1H, J=8Hz, J=10Hz), 3.64 (m, 1H), 1.76 (m, 1H), 0.94 (dd, 6H, J=8Hz, J=12Hz).

(S)-4-(1-Methylethyl)-3-(-1-oxopropionyl)-2-oxazolidone (154).[74]

n-Butylithium (40.1 mL, 1.57 M in hexane) was added dropwise (syringe pump) to a cold (-78°C) solution of oxazolidone **153** (8.1533 g, 63.13 mmol) in THF (230 mL) over a period of 30 min.

The solution was stirred at -78°C for a further 30 min and propionyl chloride (5.5 mL, 63.13 mmol) in THF (20 mL) was added dropwise (syringe pump) over 30 min. The reaction mixture was stirred at -78°C for 45 min, warmed to 0°C over about 15 min, and stirred for another 75 min at 0°C. Saturated aqueous ammonium chloride solution (5 mL) was added and the THF was evaporated from the mixture. The residue was partitioned between ether (100 mL) and saturated aqueous sodium bicarbonate (30 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was distilled to give **154** (10.3845 g, 89%): bp, 162-166°C (17 mm).

(S, S)-4-(1-Methylethyl)-3-(2-2-methyl-1-oxo-4-pentenyl)-2-oxazolidone (155).[73]

n-Butyllithium (30.2 mL, 1.57 M in hexane) was added dropwise over 5 min (syringe pump) to a cooled (0°C) solution of diisopropylamine (7.9 mL, 56.15 mmol) in THF (100 mL). The solution was stirred at 0°C for 10 min and then cooled to -78°C. Oxazolidone **154** (8.00 g, 43.19 mmol) in THF (15 mL) was added dropwise (syringe pump) over 10 min and the solution was stirred at -78°C for a further 10 min. Allyl bromide (11.2 mL, 129.56 mmol) was then added in one portion. The cold bath was removed and the reaction mixture stirred for 2 h. Saturated aqueous ammonium chloride (7 mL) was added. The organic phase was washed with 10% HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel (5x20 cm, 1:3 ethylacetate- hexane) and distilled to give **155** (7.11 g, 73%): bp, 172-176°C (17 mm); $[\alpha]_D^{25}$ +60.2° (1.71, CH_2Cl_2), (lit.[73] $[\alpha]_D$ +62.9 (3.48, CH_2Cl_2)); NMR ($CDCl_3$, 400

MHz): δ 5.80 (m, 1H), 5.08 (m, 2H), 4.48 (m, 1H), 4.28 (dd, 1H, J=8Hz), J=12Hz), 4.22 (dd, 1H, J=12Hz, J=4Hz), 3.90 (m, 1H), 2.50 (m, 1H), 2.34 (m, 1H), 2.22 (m, 1H), 1.16 (d, 3H, J=8Hz), 0.90 (dd, 6H, J=8Hz, J=16Hz); ^{13}CNMR ($CDCl_3$, 50.32 MHz): δ 175.40 (s), 153.67 (s), 135.22 (d), 116.99 (t), 63.10 (t), 58.44 (d), 38.16 (t), 37.12 (d), 28.40 (d), 17.91 (q), 16.16 (q), 14.64 (q); IR (film): 1780, 1690 cm^{-1}.

(S, S)-3-(3-(1,3)-Dioxolan-2-yl))-2-methyl-1-oxopropyl-4(-1-methylethyl)-2-oxazolidone (157).

Ozone was bubbled through a cold solution of **155** (3.98 g, 17.68 mmol) in methanol (20 mL) for 5.2 h (1.1 eq). The excess of ozone was removed with a stream of argon and dimethyl sulfide (2 mL) was added. The cold bath was removed, and the solution warmed to room temperature over 30 min. The solvent was removed and the residue was dissolved in benzene (50 mL). Ethylene glycol (8 mL) and a catalytic amount of p-toluenesulfonic acid were added. The reaction mixture was refluxed for 36 h using a Dean-Stark apparatus filled with molecular sieves (3A). The mixture was cooled, and 3A molecular sieves (250 mg) were added and stirring was continued for 30 min. The reaction mixture was filtered and the benzene was evaporated. The residue was partitioned between ether (50 mL) and saturated aqueous sodium bicarbonate (30 mL). The organic phase was washed with water (30 mL) and brine (30 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed over silica gel (3x20 cm, 2:5 ethylacetatehexane) to give **157** (3.28g, 68%) as a white solid: mp. 52-53°C. NMR ($CDCl_3$, 200 MHz): δ 4.94 (dd, 1H, J=4Hz, J=6Hz), 4.44 (m, 2H),

4.05 (m, 1H), 3.84 (m, 4H), 2.35 (m, 2H), 1.76 (dt, 1H, J=4Hz, J=14Hz), 1.20 (d, 3H, J=8Hz), 0.90 (m, 6H); ^{13}CNMR ($CDCl_3$, 50.32 MHz): δ 176.64 (s), 153.56 (s), 102.76 (d), 64.96 (t), 64.47 (t), 62.84 (t), 58.53 (d), 37.38 (t), 32.81 (d), 28.08 (d), 18.04 (q), 17.87 (q), 17.34 (q); IR (film); 1770, 1690 cm^{-1}; exact mass m/e 271.1414 (calcd for $C_{13}H_{21}NO_5$, 271.3164); Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.35; H, 7.70; N, 5.05.

(R)-2-(2-Methyl-but-3-enyl)-1,3-dioxolane (150).

Oxazolidone **157** (3.2 g, 11.79 mmol) in THF (14 mL) was added dropwise to a cooled (0°C) suspension of lithium aluminum hydride (1.34 g, 35.38 mmol) in THF (40 mL) over 5 min. The solution was stirred at 0°C for 15 min, the ice bath was removed, and stirring was continued for 40 min. The reaction mixture was cooled to 0°C and Celite (3.5 g) was added. Water (3 mL), 10% (w/v) aqueous sodium hydroxide (3 mL), and water (30 mL) were added and the white solid was filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated to give crude alcohol **158** (1.41 g, 82%) that was about 90% pure (NMR).

Oxalyl chloride (0.85 mL, 9.78 mmol) was dissolved in dichloromethane (15 mL) and cooled to -78°C. Dimethyl sulfoxide (1.4 mL, 17.78 mmol) in dichloromethane (5 mL) was added dropwise (syringe pump) over a period of 10 min. The solution was stirred for 10 min at -78°C and crude alcohol **158** in dichloromethane (5 mL) was added dropwise (syringe pump) and stirred for another 30 min. Triethylamine (6.2 mL, 44.50 mmol) was added dropwise and the solution was stirred at -78°C

for 5 min. The solution was allowed to warm slowly to room temperature over ca. 45 min. Water (10 mL) was added and the reaction mixture was extracted with dichloromethane. The aqueous phase was washed with dichloromethane (20 mL). The combined organic phases were washed successively with 10% HCl (30 mL), water (20 mL), saturated aqueous sodium bicarbonate (30 mL), water (20 mL), and dried ($MgSO_4$). The dichloromethane was removed by distillation through a Vigreaux column and the residue was chromatographed over silica gel (3x20 cm, 2:5 ether-dichloromethane). The solvent again was removed by distillation through a Vigreaux column and the crude aldehyde **159** was dissolved in THF (10 mL). Methyltriphenylphosphonium bromide (3.16 g, 8.89 mmol) in THF (50 mL) was cooled to 0°C and n-butyllithium (6 mL, 1.49 M in hexane) was added dropwise. The dark orange-brown solution was stirred for 1 h and the aldehyde solution was added dropwise over 5 min. The reaction was allowed to proceed for 1 h at room temperature. The mixture was poured into water and the aqueous phase was extracted with ether (2x30 mL). The combined organic phases were washed with brine (1x40 mL), dried ($MgSO_4$), and concentrated by normal distillation through a Vigreaux column. The residue was chromatographed over silica gel, 3x20 cm, 1:5 ether-pentane) to give **150** (759 mg, 45%) from oxazolidone **157** bp, 102-108°C (700 mm); $[\alpha]_D^{25}$ -0.91 (4.09, $CHCl_3$); NMR ($CDCl_3$, 200 MHz): δ 5.74 (m, 1H), 4.96 (m, 2H), 4.86 (t, 1H, J=6Hz), 3.96 (m, 2H), 3.84 (m, 2H), 2.40 (m, 1H), 1.66 (m, 2H), 1.05 (d, 3H, J=8Hz); ^{13} CNMR ($CDCl_3$, 100.64): δ 143.76 (d), 112.83 (t), 103.45 (d), 64.70 (t), 40.49 (t), 34.00 (d), 20.49 (q); IR (Film): 1640 cm^{-1}; exact mass m/e 142.1436 (calcd for $C_8H_{14}O_2$ 142.1966).

(S)-4-(1-Methylethyl)-3-(1-oxobutyl)-2-oxazolidone (162)[77]

n-Butyllithium (44 mL, 1.55 M in hexane, 2,2'-dipyridyl as indicator) was added dropwise (syringe pump) to a cold (-78°C) solution of oxazolidone **153** (10.0 g, 77.42 mmol) in THF (270 mL) under argon over 30 min. The solution was stirred at -78°C for a further 30 min and butyryl chloride (8 mL, 77.42 mmol) in THF (15 mL) was added (via syringe pump) over 30 min. The reaction mixture was stirred at -78°C for 30 min, warmed to 0°C over about 10 min, and stirred for another 30 min at 0°C. Saturated aqueous ammonium chloride (10 mL) was added. The organic phase was separated and washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was distilled to give oxazolidone **162** (14.05 g, 91%) which was homogeneous by TLC (silica, 2:5, ethylacetate-hexane): bp, 166-168°C (17 mm); NMR ($CDCl_3$, 400 MHz): δ 4.35 (m, 1H), 4.15 (m, 2H), 2.90 (m, 1H), 2.80 (m, 1H), 2.35 (m, 1H), 1.68 (m, 2H), 0.97 (t, 3H, J=9Hz), 0.89 (dd, 6H, J=8Hz, J=16Hz); ^{13}CNMR ($CDCl_3$, 50.32): δ 179.50 (s), 153.14 (s), 63.30 (t), 58.32 (d), 37.28 (t), 23.38 (d), 17.90 (q), 17.84 (t), 14.62 (q), 13.57 (q); IR (film): 1770, 1690 cm^{-1}; exact mass m/e 199.1205 (calcd for $C_{10}H_{17}NO_3$, 199.2514); Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.54; H, 8.56; N, 6.67.

(S, S)-3-(2-Ethyl-1-oxo-4-pentenyl)-4-(1-methylethyl)-2-oxazolidone (163).[77]

n-Butyllithium (29.0 mL, 1.47 M in hexane) was added dropwise over 10 min (syringe pump) to a stirred solution of diisopropylamine

(S)-4-(1-Methylethyl)-3-(1-oxobutyl)-2-oxazolidone (162)[77]

n-Butyllithium (44 mL, 1.55 M in hexane, 2,2'-dipyridyl as indicator) was added dropwise (syringe pump) to a cold (-78°C) solution of oxazolidone **153** (10.0 g, 77.42 mmol) in THF (270 ml) under argon over 30 min. The solution was stirred at -78°C for a further 30 min and butyryl chloride (8 ml, 77.42 mmol) in THF (15 mL) was added (via syringe pump) over 30 min. The reaction mixture was stirred at -78°C for 30 min, warmed to 0°C over about 10 min, and stirred for another 30 min at 0°C. Saturated aqueous ammonium chloride (10 mL) was added. The organic phase was separated and washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was distilled to give oxazolidone **162** (14.05 g, 91%) which was homogeneous by TLC (silica, 2:5, ethylacetate-hexane): bp, 166-168°C (17 mm); NMR ($CDCl_3$, 400 MHz): δ 4.35 (m, 1H), 4.15 (m, 2H), 2.90 (m, 1H), 2.80 (m, 1H), 2.35 (m, 1H), 1.68 (m, 2H), 0.97 (t, 3H, J=9Hz), 0.89 (dd, 6H, J=8Hz, J=16Hz); ^{13}CNMR ($CDCl_3$, 50.32): δ 179.50 (s), 153.14 (s), 63.30 (t), 58.32 (d), 37.28 (t), 23.38 (d), 17.90 (q), 17.84 (t), 14.62 (q), 13.57 (q); IR (film): 1770, 1690 cm^{-1}; exact mass m/e 199.1205 (calcd for $C_{10}H_{17}NO_3$, 199.2514); Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.54; H, 8.56; N, 6.67.

(S, S)-3-(2-Ethyl-1-oxo-4-pentenyl)-4-(1-methyl ethyl)-2-oxazolidone (163).[77]

n-Butyllithium (29.0 mL, 1.47 M in hexane) was added dropwise over 10 min (syringe pump) to a stirred solution of diisopropyl-amine

(5.9 mL, 42.41 mmol) in THF (100 mL) that was cooled to 0°C. Stirring was continued for 10 min at 0°C and the solution was cooled to -78°C. Oxazolidone **162** (6.5 g, 32.62 mmol) in THF (20 mL) was added dropwise over 15 min. Stirring at -78°C was continued for a further 30 min, and allyl bromide (8.5 mL, 97.87 mmol) was then added in one portion. The cooling bath was removed, and the mixture was stirred for 2 h at room temperature. Saturated aqueous ammonium chloride (10 mL) was added. The organic phase was separated, washed with 10% HCl (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel (5x25 cm, 1:3 ethylacetate-hexane) and distilled to give **163** (6.15 g, 79%): bp, 164-168°C (17 mm); $[\alpha]_D^{25}$ +78.30° (1.08, $CHCl_3$), (lit.[77] $[\alpha]_D^{20}$ +82.47 (6.81, $CHCl_3$)); NMR ($CCDl_3$, 200 MHz): δ 5.80 (m, 1H), 5.10 (m, 2H), 4.48 (m, 1H), 4.25 (m, 2H), 3.90 (m, 1H), 2.40 (m, 3H), 1.64 (m, 2H), 0.99 (m, 9H); ^{13} CNMR ($CDCl_3$, 50.32 MHz): δ 175.78 (s), 153.72 (s), 135.28 (d), 116.81 (t), 62.98 (d), 58.81 (d), 43.71 (d), 36.42 (t), 28.36 (d), 24.41 (t), 17.92 (q), 14.57 (q), 11.51 (q); IR (film): 1775, 1690, 1640 cm^{-1}; exact mass m/e 239.1520 (calcd for $C_{13}H_{21}NO_3$ 239.3172); Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.03; H, 8.65, N, 5.71.

(S, S)-3-(3-(1,3-Dioxolan-2-yl))-2-ethyl-1-oxopropyl-4-(1-methylethyl) -2-oxazolidone (164).

Ozone was bubbled through a cold (-78°C) solution of oxazolidone **162** (5.38 g, 22.47 mmol) in methanol (20 mL) for 6.4 h (1.1 eq). Excess of ozone was removed by a stream of argon and

dimethyl sulfide (4 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over 15 min. The solvent was evaporated and the residue was dissolved in benzene (35 mL). Ethylene glycol (10 mL) and a catalytic amount of p-toluenesulfonic acid were added. The reaction mixture was refluxed for 36 h using a Dean-Stark apparatus filled with molecular sieves (3A). The mixture was cooled to room temperature and 4A molecular sieves (500 mg) were added. The mixture was then stirred for 1 h and solid sodium bicarbonate (400 mg) was added, and the solids, after brief stirring, were removed by filtration. The benzene solution was evaporated and the residue was partitioned between ether (50 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic phase was washed successively with water (30 mL) and brine (30 mL), and was dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed over silica gel (5x23 cm; 2:5 ethyl acetate-hexane) to give **164** (4.37g, 68%); NMR ($CDCl_3$, 200 MHz): δ 4.95 (dd, 1H, J=4Hz, J=5Hz), 4.45 (m, 1H), 4.22 (m, 1H), 4.05 (m, 1H), 3.86 (m, 4H), 2.35 (m, 2H), 1.80 (m, 3H), 0.90 (m, 9H); ^{13}CNMR ($CDCl_3$, 50.32 MHz); δ 176.01 (s), 153.31 (s), 102.81 (d), 64.92 (t), 64.43 (t), 58.57 (d), 38.67 (d), 35.34 (t), 28.03 (d), 26.08 (t), 17.85 (q), 14.22 (q), 11.11 (q); IR (film): 1780, 1695 cm^{-1}; exact mass m/e 285.1570 (calcd for $C_{14}H_{23}NO_5$, 285.343); Anal. Calcd for $C_{14}H_{23}NO_5$; C, 58.93; H, 8.12; N, 4.91. Found: C, 59.14; H, 8.08; N. 4.75.

(R)-(2-Ethyl-3-butenyl)-1,3-dioxalone (151).

Aldehyde **164** (1.2467 g, 7.78 mmol) dissolved in THF (10 mL) was added dropwise to a cooled (0°C) suspension of lithium aluminium

hydride (497 mg, 13.11 mmol) in THF (50 mL). The reaction mixture was stirred at 0°C for 1 h. Celite (0.5 g) was added, followed by water (1.5 mL), 10% (w/v) aqueous sodium hydroxide. The resulting white solid was filtered and washed thoroughly with ether. The filtrate was dried ($MgSO_4$) and evaporated. Distillation of the residue gave the crude alcohol, (562.2 mg, 3.51 mmol) 86% pure by NNMR, which was dissolved in dichloromethane (5 mL). Dimethyl sulfoxide (0.55 ml, 7.72 mmol) in dichloromethane (5 mL) was added dropwise (syringe pump) to a cold (-78°C) solution of oxalyl chloride (.34 ml, 3.86 mmol) in dichloromethane (5 mL). The solution was stirred at -78°C for 45 min and triethylamine (2.45 mL, 17.55 mmol) was added. The solution was stirred at -78°C for 5 min more, the cold bath was removed, and the solution was allowed to warm to room temperature over 30 min. Water (20 mL) was added and the layers were separated. The aqueous phase was washed with dichloromethane (30 mL). The combined organic solutions were washed successively with 10% HCl (20 mL), water (20 mL), saturated aqueous sodium bicarbonate (20 mL), and dried ($MgSO_4$). The solution was concentrated by normal distillation through a Vigreaux column and the crude aldehyde was dissolved in THF (5 mL). n-Butyllithium (2.4 ml, 1.47 M in hexane) was added to a cooled (0°C) solution of methyltriphenylphosphonium bromide (1.25 g, 3.50 mmol) in THF (50 mL) under argon. The solution was stirred for 30 min at 0°C. The crude aldehyde solution was added to the ylide solution over 5 min and the mixture was stirred for 5 h at room temperature. The mixture was poured into water and the phases were separated. The aqueous layer was washed with ether (2x50 mL) and the combined ether extracts were washed with brine

(50 mL), dried ($MgSO_4$), and concentrated by distillation through a Vigreaux column. The residue was chromatographed over silica gel (2x17 cm, 1:5 ether-pentane) and distilled to give **151** (0.49 g, 40%) from aldehyde **164.** bp, 102-108°C (700 mm); $[\alpha]_D^{25}$ -0.091 (1.00, $CHCl_3$); NMR ($CDCl_3$, 200 MHz): δ 5.60 (m, 1H), 5.00 (m, 2H), 4.84 (t, 1H, J=6Hz), 3.95 (m, 2H), 3.80 (m, 2H), 2.15 (m, 1H), 1.66 (dd, 2H, J=6Hz, J=8Hz), 1.34 (m, 2H), 0.85 (t, 3H, J=8Hz); ^{13}CNMR ($CDCl_3$, 100.64); δ 141.95 (d), 114.74(t), 103.43 (d), 64.68 (t), 41.73 (d), 38.75 (t), 27.90 (t), 11.29 (q); IR (film): 1635 cm^{-1}; exact mass (No M^+) 127.0755 (calcd for $C_7H_{11}O_2$ (M-29) 127.1642); Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32, Found: C, 69.50; H, 10.23.

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